Studies towards the synthesis of functionalised 6H-pyrido[4,3-b]carbazoles

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STUDIES TOWARDS THE SYNTHESIS OF FUNCTIONALISED 6H-PYRIDO[4,3-b]CARBAZOLES

submitted by

PAUL D. JENKINS

for the degree of

Doctor of Philosophy

of the

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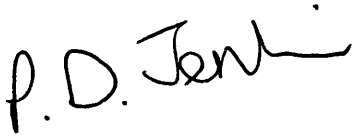

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Finally, I would like to mention my mother for her love and support over the last three years.

For my parents

SUMMARY

The work described in this thesis was carried out at the University of Bath between October 1986 and September 1989, and is concerned with the preparation of suitably functionalised carbazoles and their further elaboration to 6H-Pyrido[4,3-*b*]carbazoles.

A model study was successfully carried out for the synthesis of the natural product olivacine (2).

Thus, gramine (166) was condensed with a substituted ketone (165) to yield an intermediate (167) which was elaborated to 3-formyl-1-methyl carbazole (205). Condensation of this aldehyde (205) with aminoacetaldehyde dimethylacetal and subsequent methylation yielded 3-[N-(2,2-Dimethoxyethyl)ethylamino]-1-methylcarbazole (207).

N-Tosylation of this compound (207) and treatment with acid yielded 1,2-dihydro-1,5-dimethyl-2-(4-tosyl)-6H-pyrido[4,3-*b*]carbazole (208). Reaction of this compound (208) with sodium in liquid ammonia yielded olivacine (2).

A versatile intermediate, ethyl 3-(5-benzyloxy-3-indolyl)-2-cyanobutanoate (235) was synthesised by the acid catalysed addition of ethyl 2-cyano-but-2-enoate (240) to 5-benzyloxyindole.

This intermediate (235) can be alkylated by various substrates and then further elaborated to afford 1,3,4,6-tetrasubstituted carbazoles.

CONTENTS

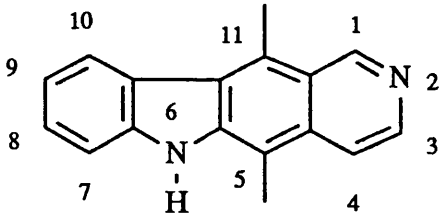
Introduction

Isolation and Biogenesis of Ellipticine and its Derivatives

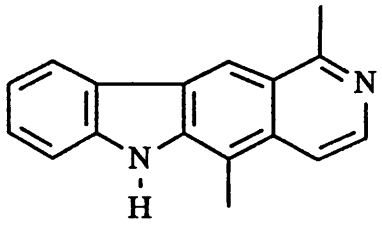
The alkaloid ellipticine, 5,11-dimethyl-6H-pyrido[4,3-*b*] carbazole (1) was first isolated in 1959[1] from the leaves of *Ochrosia elliptica Labill* (Apocynaceae), an evergreen tree which grows wild in Oceania. Subsequently, further quantities of ellipticine, along with 9-methoxyellipticine, and olivacine (2), 1,5-dimethyl-6H-pyrido[4,3-*b*] carbazole, were isolated from varoius plants in the *Aspidosperma, Ochrosia, Strychnos* and *Tabernaemontane* genera of the Apocynaceae family[2,3].

In 1967, during an examination of Australian plants for anticancer activity, ellipticine and 9-methoxyellipticine were obtained from the extracts of two other shrubs, *0. moorei F. Muell and Excavatia coccinea* (Tejs. and Bin.) Mgf[4].

Together, the two ellipticines were shown to account for the activity of the crude plant extracts towards the experimental tumours Sarcoma 180, Adenocarcinoma, and Lymphoid L1210 leukaemia implanted in mice, and human carcinoma of the nasopharynx carried in cell culture[5].

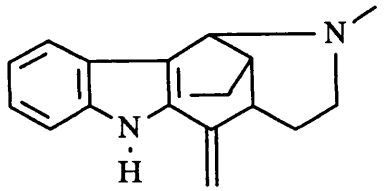


(1)



(2)

Ellipticine and its natural isomer olivacine (2) usually co-occur with uleine[6] (3) and apparacine (4)[7] (Scheme 2). It is therefore presumed that these alkaloids have the same biological progenitor[8].



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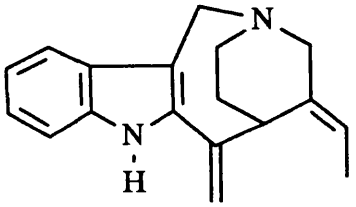
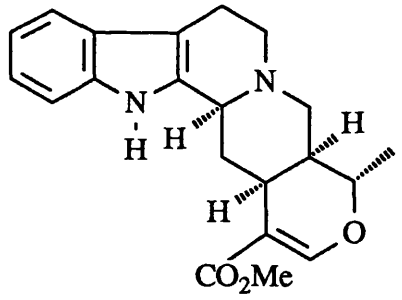


(4)

It is well established that the biosynthesis of bases, such as tetrahydroalstonine (di-desmethoxyisoreserpiline) (5), involves the coupling of a tryptamine unit [from tryptophan or tryptamine ((6), R = CO_2H, or R = H respectively)] and a C9, or C10 fragment which is terpenoid in origin and is utilised by the plant in the form of the glucoside secologanine[9,10] (7).



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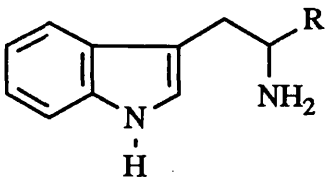
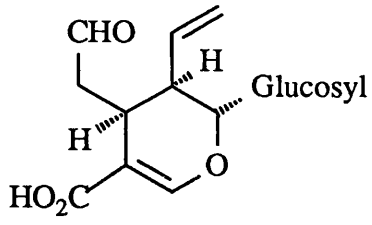


(6)

The major obstacle to discerning the link between the ellipticines and the main body of indole alkaloids is the fact that in the former, three carbon atoms separate the indolic-3-position and the pyridine N-atom. In the typical indolic bases, the tryptamine unit is preserved intact, and only two carbon atoms are interposed between the 3-indole carbon atom and the basic nitrogen atom of the piperidine ring. This problem has generated some debate and some experimental work but the question of how the two biosynthetic processes are related is still not fully understood.



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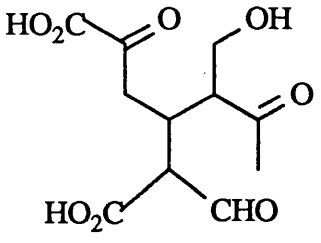


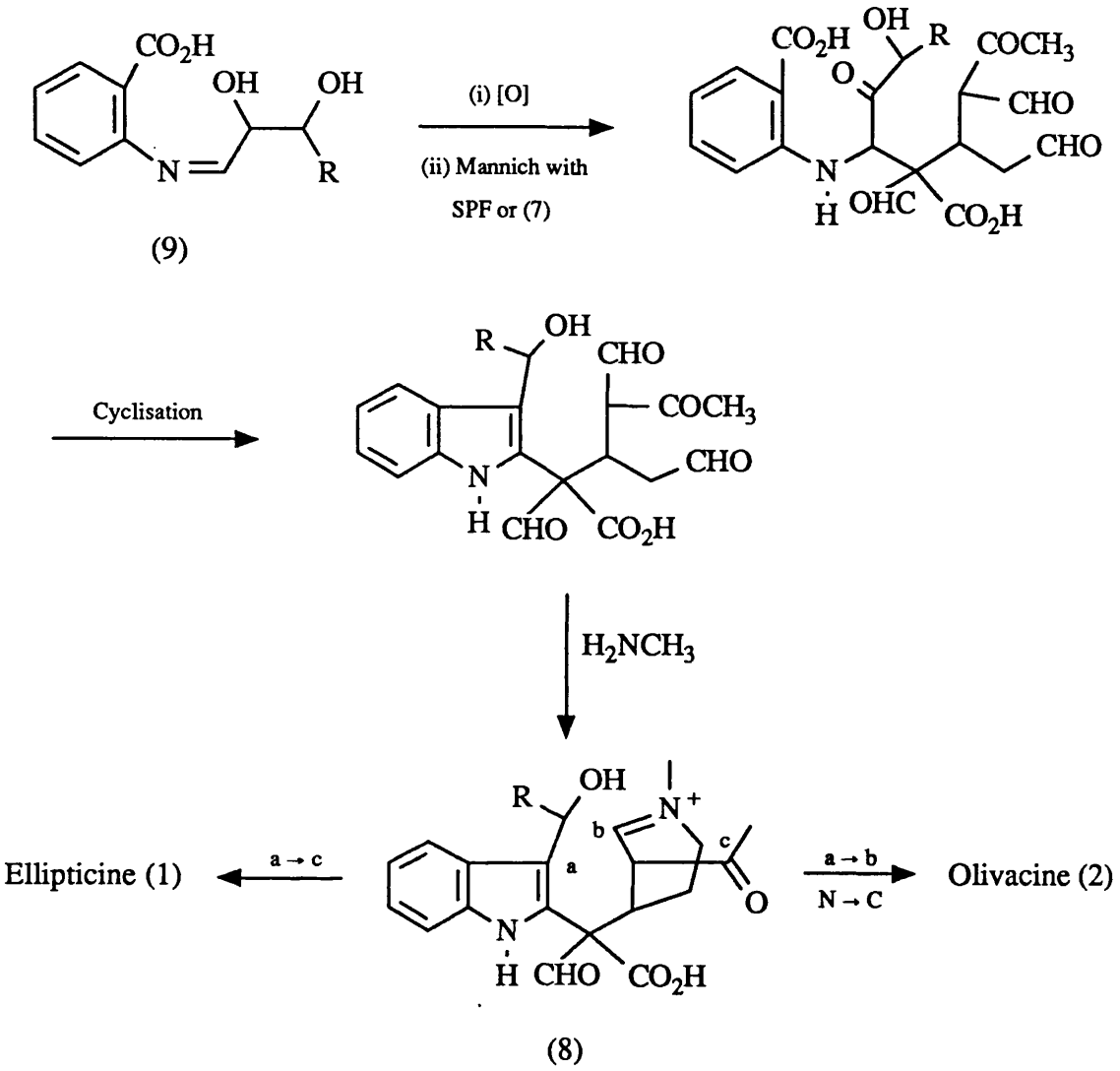
(10)

The first detailed proposal on the biogenesis of ellipticine and related alkaloids was by Wenkert[11]. He postulated a common precursor (8) (Scheme 1), derived from glycosylidene anthranilic acid (9), a tryptophan progenitor, and a *seco*-prephenateformaldehyde (SPF) unit (10) or secologanine (7), as possible biogenetic intermediates for these alkaloids. Cyclisation of an SPF unit at C-19 (c) or C-21 (b) with the indolic β-position (a), followed by extrusion (via *retro*-aldolisation of the β-glycosyl function) could give rise to the *Aspidosperma* skeleta of ellipticine (1), olivacine (2) and uleine (3) (Scheme 1). It should be noted that apparacine (4) is not included.

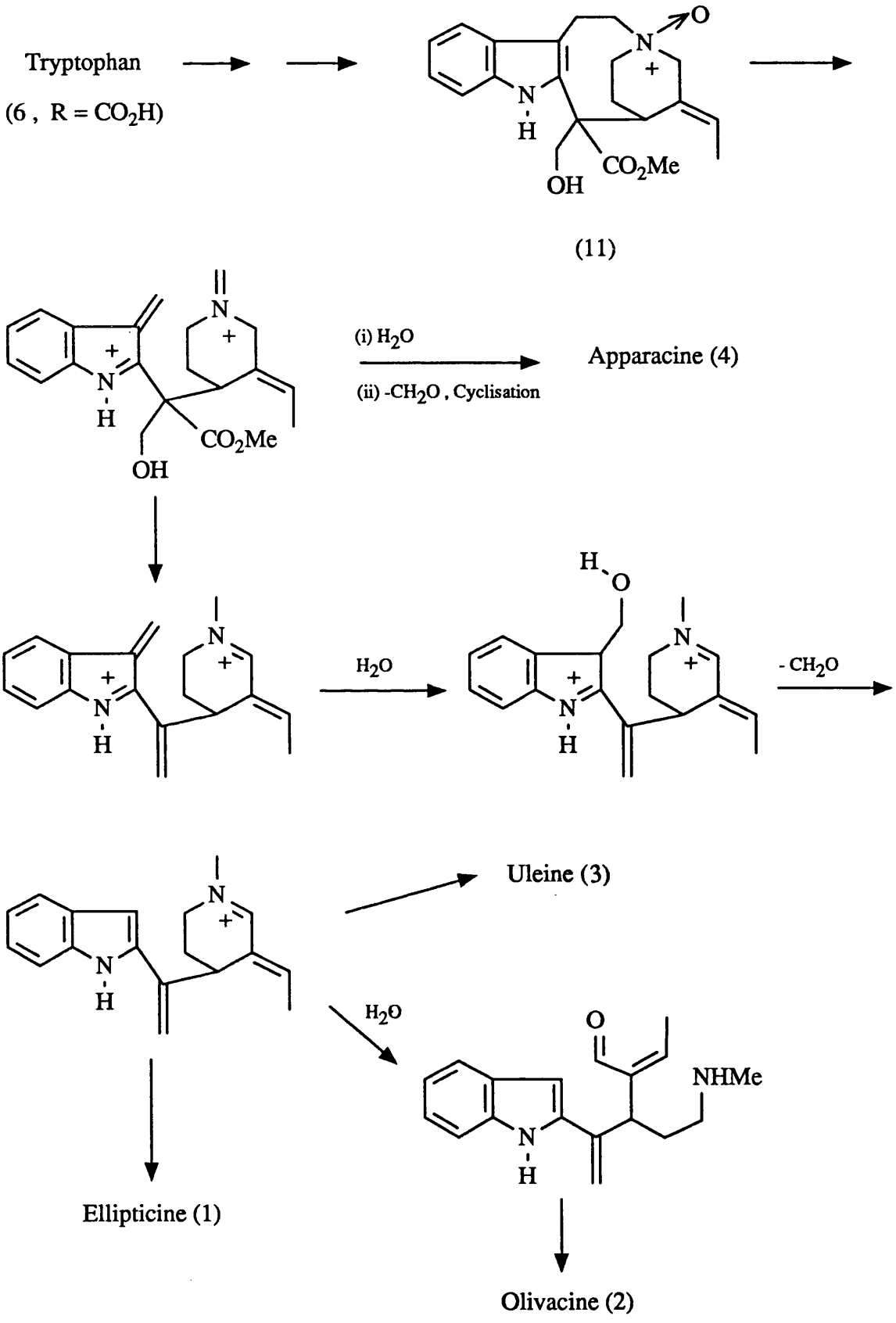
The most recent and widely accepted hypothesis was postulated by Potier and Janot[12]. They envisaged that stemmadenine-N-oxide (11) is the key intermediate. This is then presumed to undergo a modified Polonovski type reaction[13-16] to give a number of indolenium products which can cyclise to the four congeners ellipticine (1), olivacine (2), apparacine (4) and uleine(3) (Scheme 2).

As stated earlier, tryptophan is considered to be the usual source of the indole ring of most alkaloids and there has been some controversy over which, if either, scheme is correct.

Labelling experiments with both tryptophan and stemmadenine indicated a significant incorporation of both these compounds into apparacine (4). However, a very weak incorporation of tryptophan and stemmadenine was observed for uleine (3) and none at all for


CO2H
OH
OH
N
R
(i) [O]
(ii) Mannich with
SPF or (7)
CO2H
OH
R
COCH3
O
CHO
CHO
N
H
OHC
CO2H
(9)
Cyclisation
R
OH
CHO
COCH3
CHO
N
H
CHO
CO2H
H2NCH3
R
OH
N+
b
c
a
N
H
CHO
CO2H
O
Ellipticine (1)
a → c
a → b
N → C
Olivacine (2)
(8)
a → b
Uleine (3)

Scheme 1


Tryptophan
(6 , R = CO2H)
(11)
(i) H2O
(ii) -CH2O , Cyclisation
Apparacine (4)
H2O
- CH2O
Uleine (3)
H2O
NHMe
Ellipticine (1)
Olivacine (2)

Scheme 2

both ellipticine and olivacine.[17,18] The incorporation of labelled substrates into higher plants, however, is notoriously difficult so this result is not surprising.

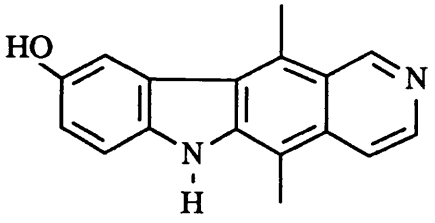
In the light of these observations, the Potier and Janot hypothesis seems more attractive at the present time, although further experimental support is still required to show its validity.

Syntheses of Ellipticine and its Analogues

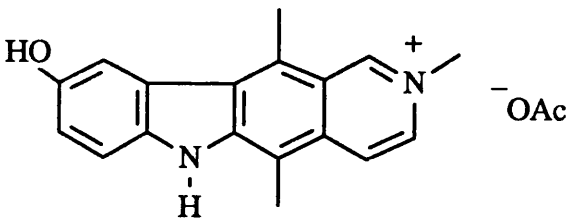
The synthesis of ellipticines has been the subject of continuous research for the last thirty years, and these efforts have been thoroughly reviewed through to March 1985.[19-21,8]

Hence, this introduction will only pick out these syntheses which highlight the various approaches to the tetracyclic system and cover any new syntheses reported since the last review.

It has been shown that 9-hydroxyellipticine (12), a major metabolite of ellipticine in the rat[22], is forty times more active than ellipticine against leukaemia L1210 implanted in mice[23,24] and recently, other more active ellipticine derivatives have also been reported.[25]



(12)



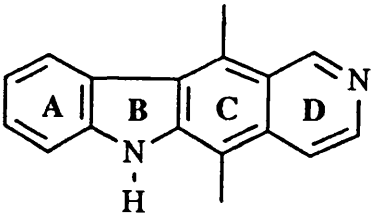
(13)

9-Hydroxyellipticine (12), in the form of its metho salt (13), has proceeded through clinical trials to its use in France for the treatment of human solid tumours. However, in Britain and the United States, there remains doubts about the long term toxicity of these

drugs, especially their mutagenic action. Therefore, to date, no ellipticine analogue has received recognition as a major drug.

As a result, current synthetic interests have shifted towards the construction of derivatives that contain substituents more likely to impart even greater activity or to improve solubility in aqueous media.

Sainsbury[19] has classified the synthetic approaches to ellipticines into three classes: B, C and D, based upon the last ring to be constructed. Since a new synthetic method[26] involving the simultaneous construction of two rings (B+C) has recently been discovered, routes to ellipticines can be classified into four classes B,C,D and B+C.



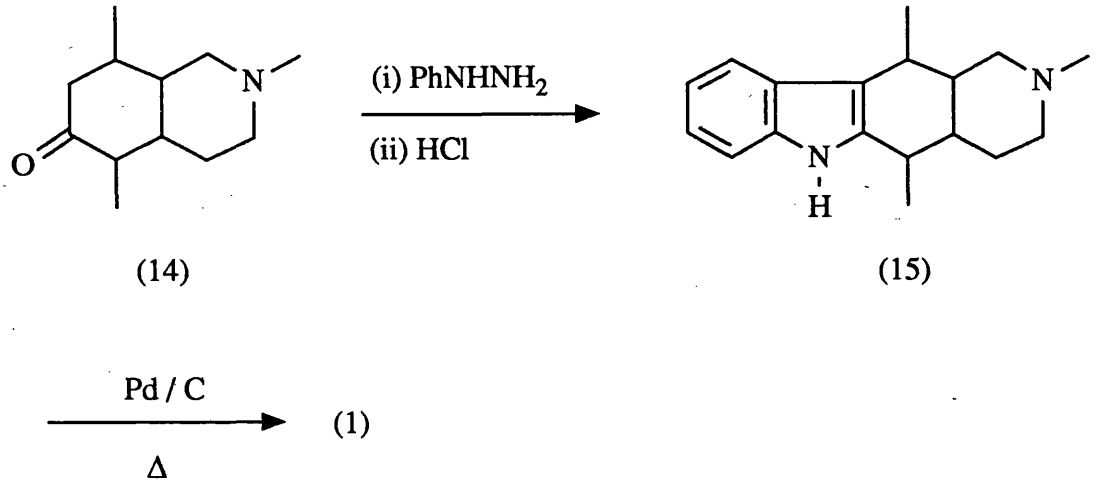
(1)

As the ellipticine molecule is now readily accessible by total synthesis,new synthetic methodology is evolving which allows direct and specific functionalisation. Hence, an additional classification will be contained in this introduction, covering the general derivatization of ellipticine.

B-Type Syntheses

This bond forming strategy was first employed by Woodward and Stillwell[27] who used a Fischer indolisation reaction to synthesise an octahydroellipticine (15) in 82% yield from the decahydroisoquinolin-6-one (14). N-Demethylation and oxidation was effected by hydrogenolysis over palladium on charcoal. (Scheme 3). Although the initital reaction was

very efficient, the final N-demethylation/oxidation process only produced ellipticine (1) in 0.3% yield.

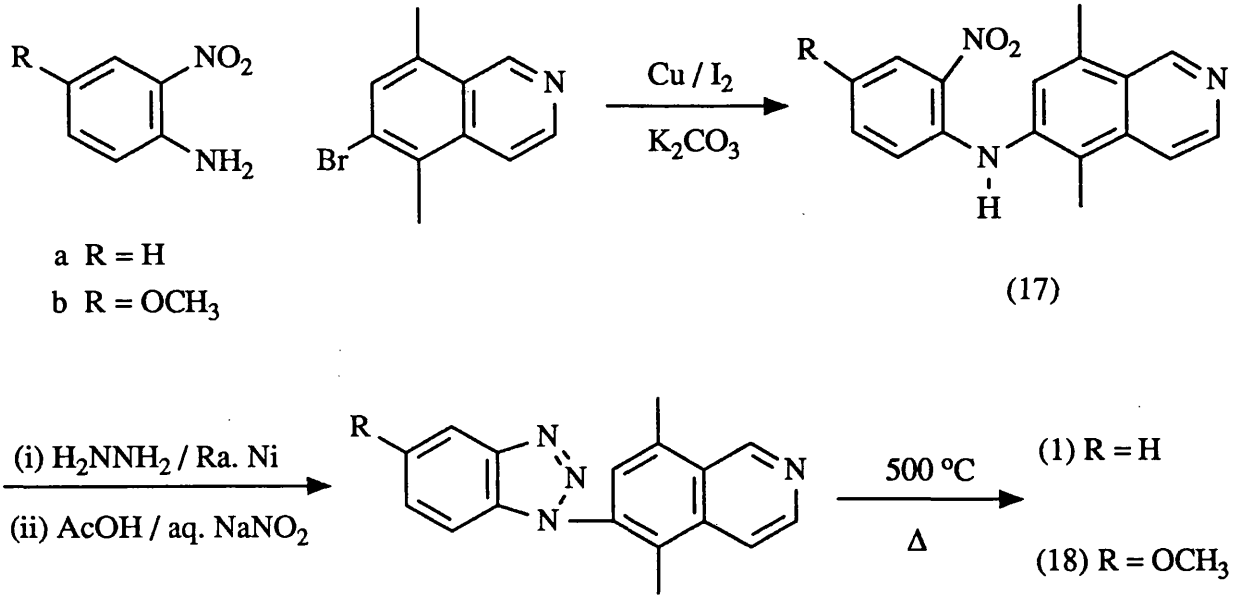


Scheme 3

Miller *et al.*[28,29] reported a B-type synthesis using the benzotriazoles (16a) and (16b) as key intermediates. (This approach was originally employed by Bisagni *et al.*[30-33] for the synthesis of 9-azaellipticine). (Scheme 4).

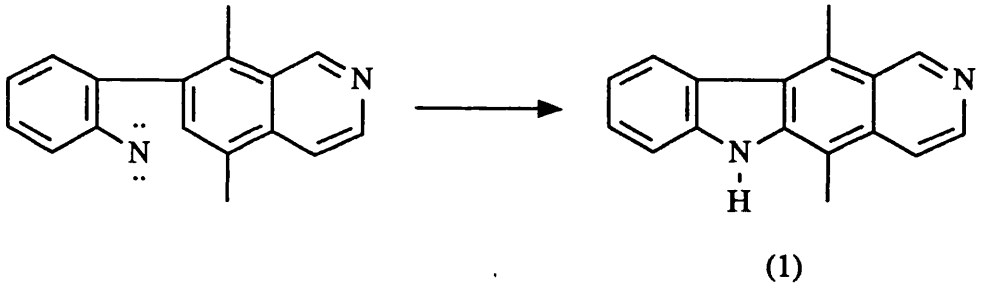
Thus, substituted nitroanilines were coupled with 6-bromo-5,8-dimethylisoquinoline, under Goldberg conditions, to yield the corresponding diarylamines (17a) and (17b) in 54% and 53% yield respectively. Reduction of the nitro group with hydrazine hydrate-Raney nickel, followed by diazotisation gave the required benzotriazoles (16a) and (16b) in yields of 97% and 94% respectively. Pyrolytic decomposition of these intermediates at 500°C yielded ellipticine (1) and 9-methoxyellipticine (18) in yields of 69% and 62% respectively.

The major criticisms of this synthesis are the difficulties in obtaining large supplies of the bromoisoquinoline and the harsh conditions employed in the final pyrolysis step.



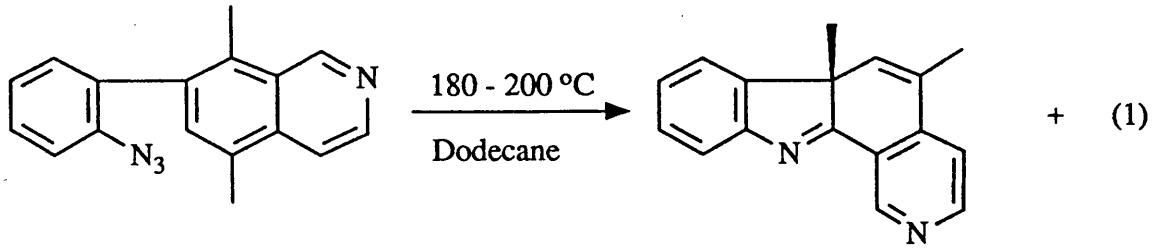
Scheme 4

Recently, Miller and co-workers[29] devised a synthetic approach to ellipticine (1) involving a nitrene insertion. (Scheme 5).



Scheme 5

The azido compound (19) was chosen as the nitrene precursor. However, on heating in dodecane at 180-200°C, two products were isolated. The minor product (20% yield) was identified as ellipticine (1). Unfortunately the major product was characterised as the 3,3-disubstituted indolenine (20). (Scheme 6).



(19) (20)

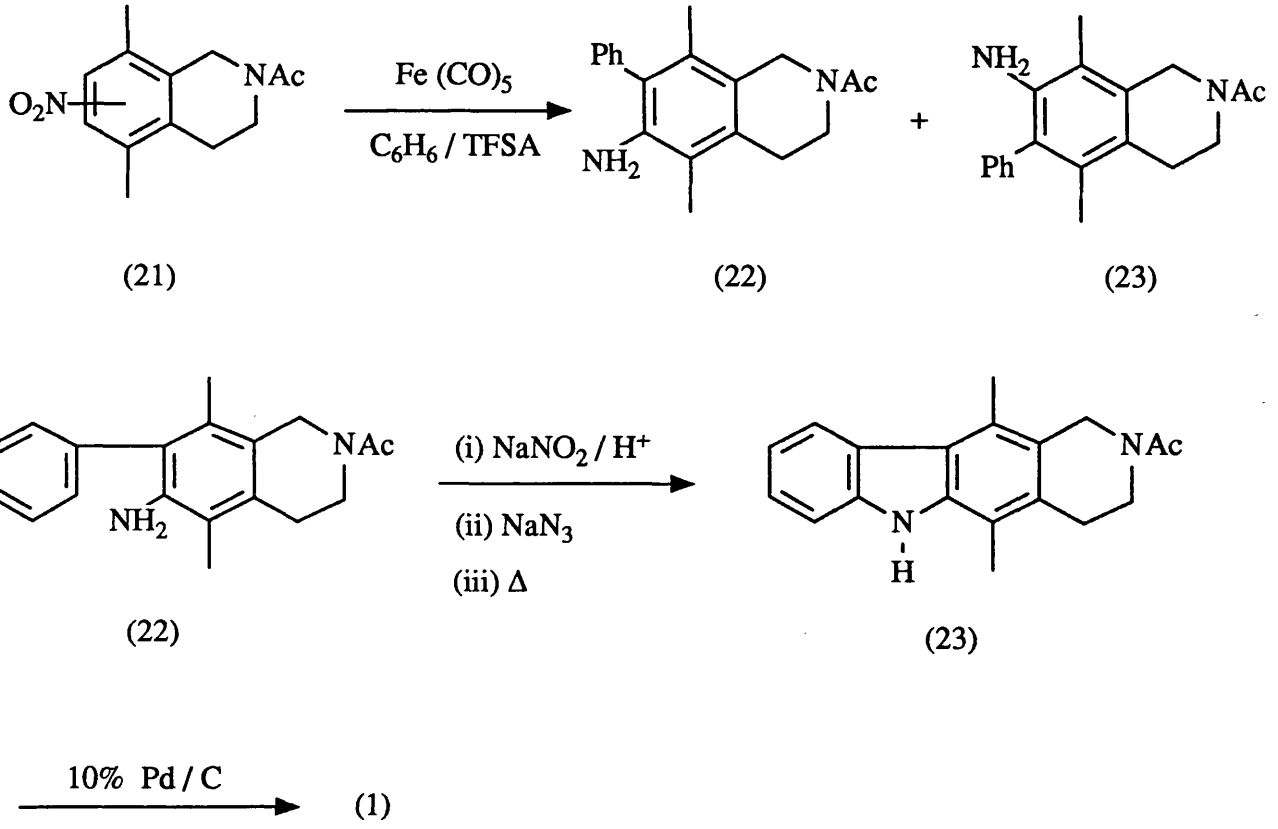
Scheme 6

A similar approach had been developed by Shudo *et al.*[34]

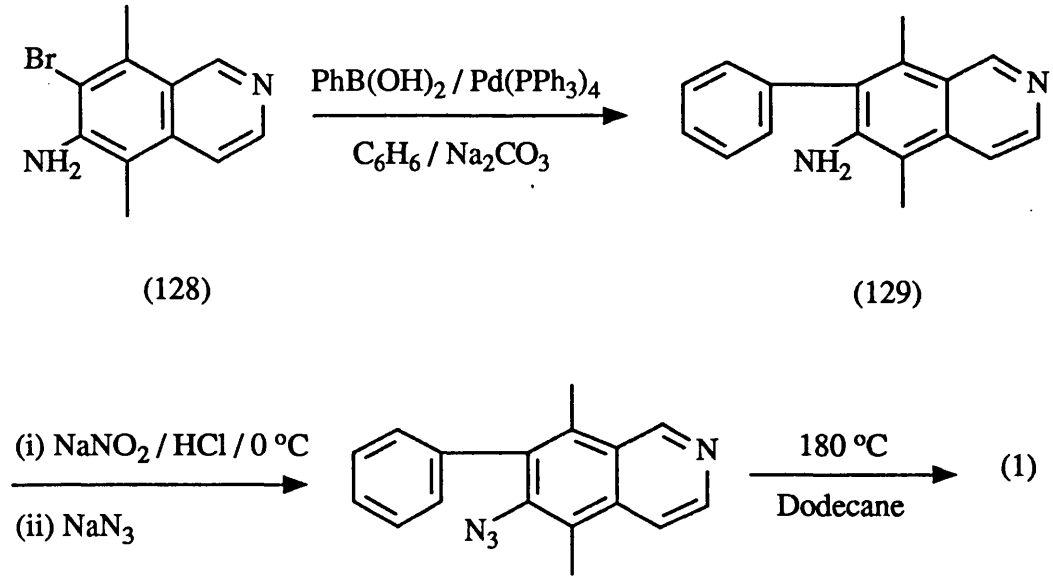
These workers had devised a procedure for the reductive phenylation of nitroarenes and successfully applied the method to the synthesis of ellipticine (1).

Treatment of an inseparable mixture of 2-acetyl-1,2,3,4-tetrahydro-5,8-dimethyl-6-nitroisoquinoline and 2-acetyl-1,2,3,4-tetrahydro-5,8-dimethyl-7-nitroisoquinoline (21) in benzene and trifluoromethanesulphonic acid (TFSA) with iron pentacarbonyl gave the phenylaminotetrahydroisoquinolines (22) (44%) and (23) (22%). Conversion of the primary amine in (22) to an azide function, followed by a thermal cyclisation furnished the intermediate (23) (43%), which was aromatised to ellipticine (1) in 46% yield by using 10% Pd/C. (Scheme 7).

Miller *et al*[35] have further extended this methodology by synthesising the aminobromoisoquinoline (128) and, using the methodology of Suzuki[36], effecting a coupling with phenylboronic acid to afford 6-amino-5,8-dimethyl-7-phenylisoquinoline (129) (99%). The amine (129) was converted to the azide (130) (85%), which was subjected to solvent phase thermolysis to afford ellipticine (1) (99%). (Scheme 8).



Scheme 7



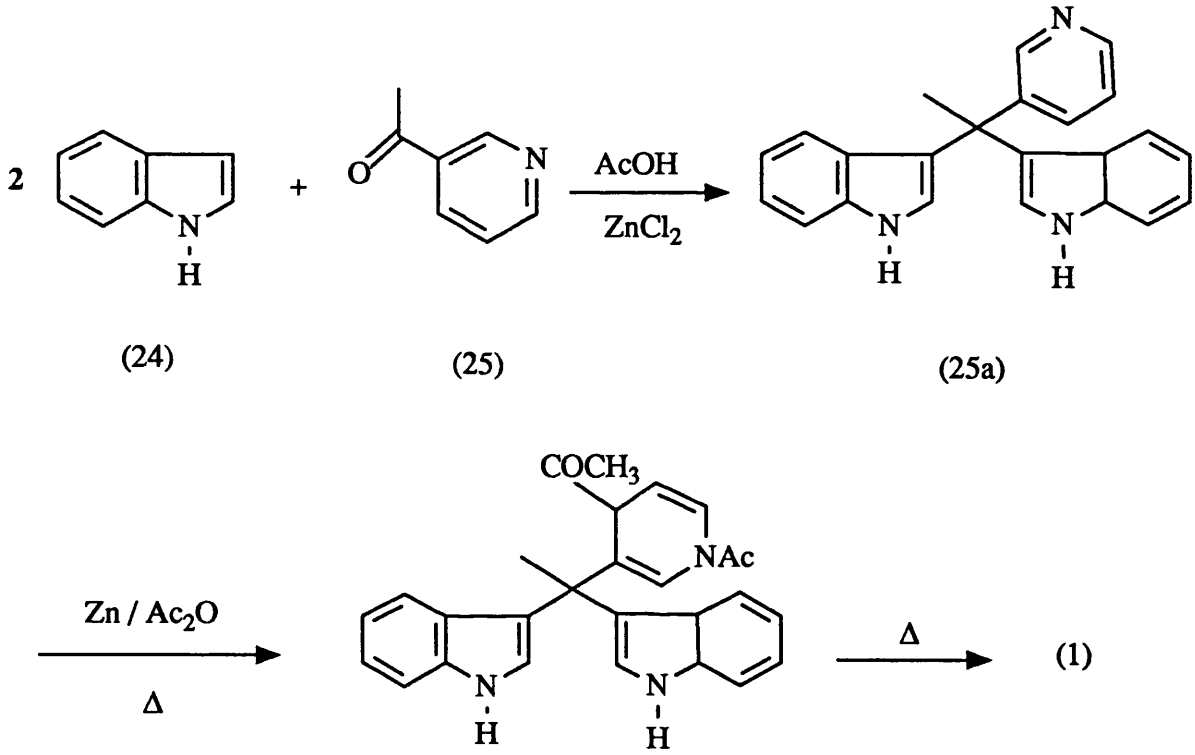
(130)

Scheme 8

C-Type Synthesis

This class has produced the most synthetic routes to date.

Woodward[37] was the first to see the attractiveness of using indole (24) and 3-acetylpyridine (25) as starting materials. (Scheme 9) However, the overall yield of the synthesis was less than 2%. Consequently, the synthesis has never been used but its simplicity has served as an inspiration for other workers.

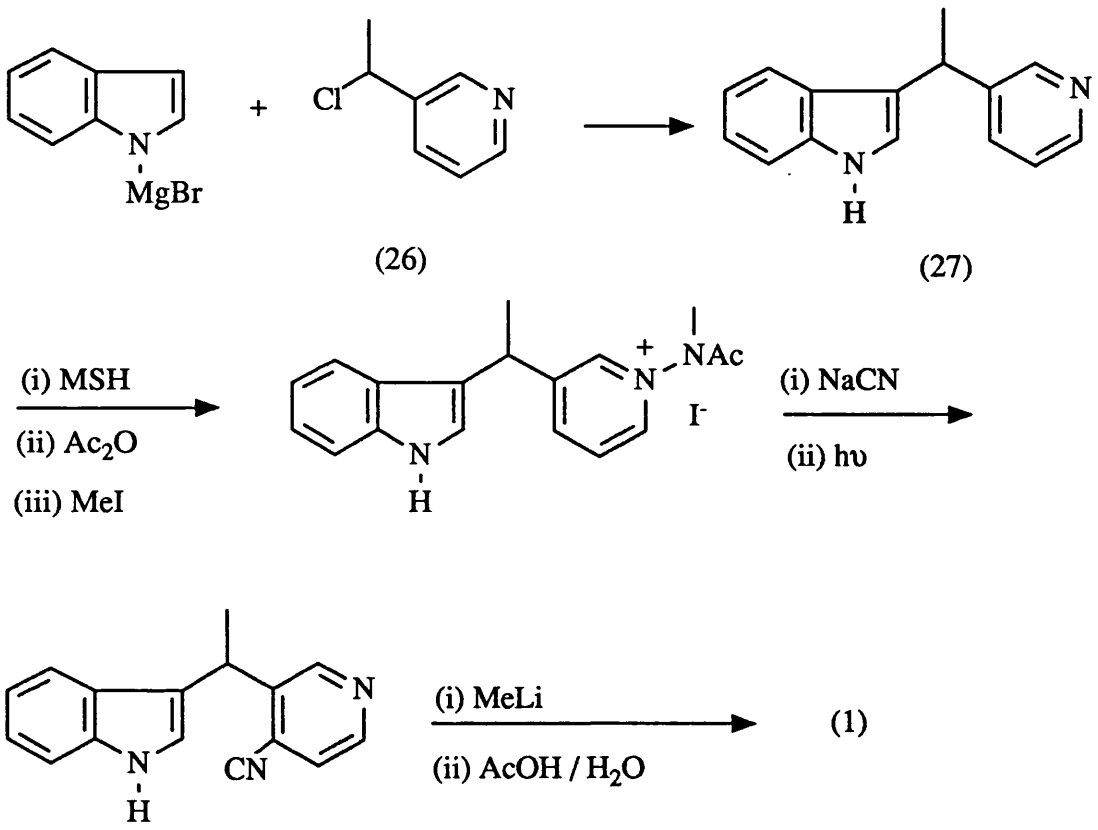


Scheme 9

Sainsbury[38] pointed out that the extra indolyl unit is only removed with difficulty, under pyrolytic conditions, in the final oxidative cyclization (Scheme 9). He consequently developed an approach to ellipticine, in which indole magnesium bromide is reacted with 3-(1-chloroethyl)pyridine (26) to yield the adduct (27). (Scheme 10).

Functionalisation of the pyridine nitrogen of this adduct (27) with O-mesitylene sulphonyl hydroxylamine (MSH), acetic anhydride and methyl iodide facilitates the already

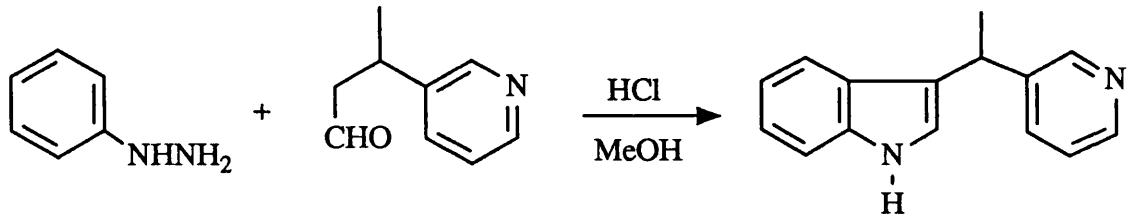
electron deficient pyridine ring to regioselective nucleophilic attack by sodium cyanide. This gives a dihydropyridine intermediate which degrades on photolysis to yield the nitrile (28). Treatment of the nitrile (28) with methyllithium and subsequent mild hydrolysis, with dilute acetic acid, afforded ellipticine (1).



Scheme 10

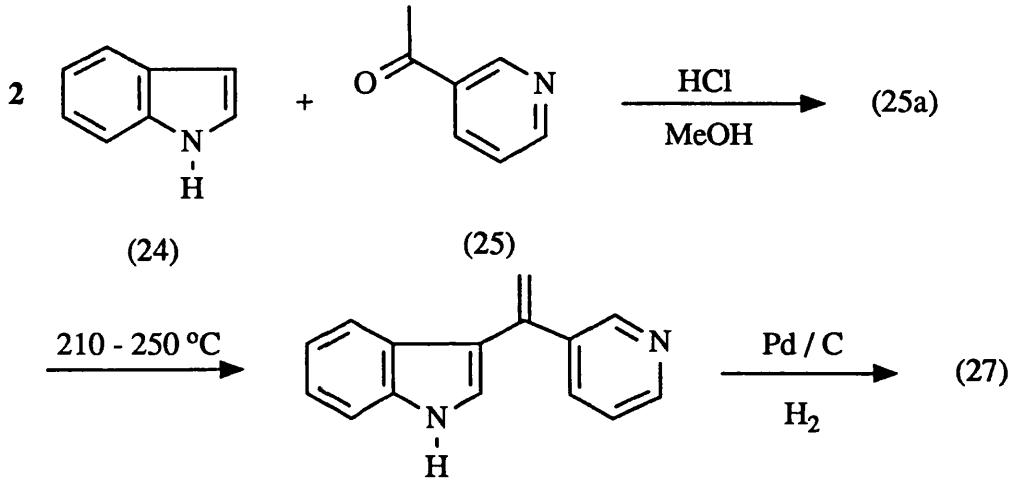
Sainsbury *et al.*[39] have reported an improved synthesis of the key intermediate (27), using a Fischer indolisation reaction upon the accessible aldehyde (29). (Scheme 11).

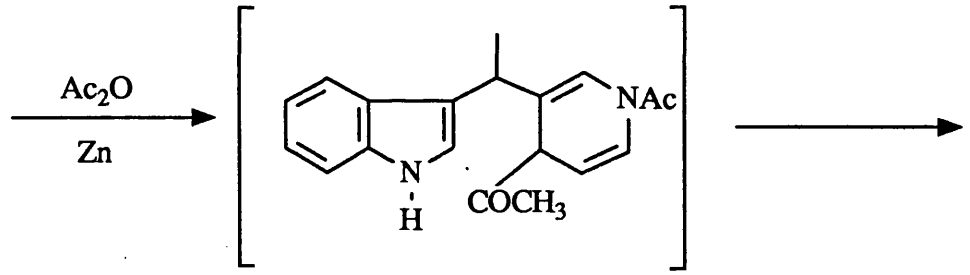
More recently, Chinese workers[40] have prepared the intermediate (27) in a three step procedure in an overall yield of 36%. (Scheme 12).



(29) (27)

Scheme 11





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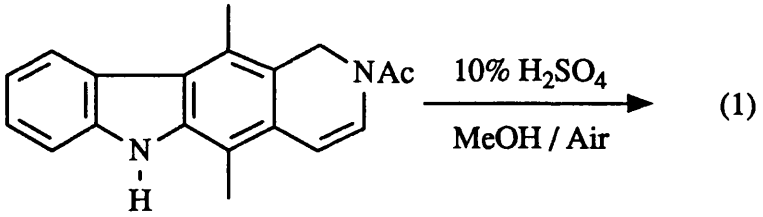


(33)

Scheme 12

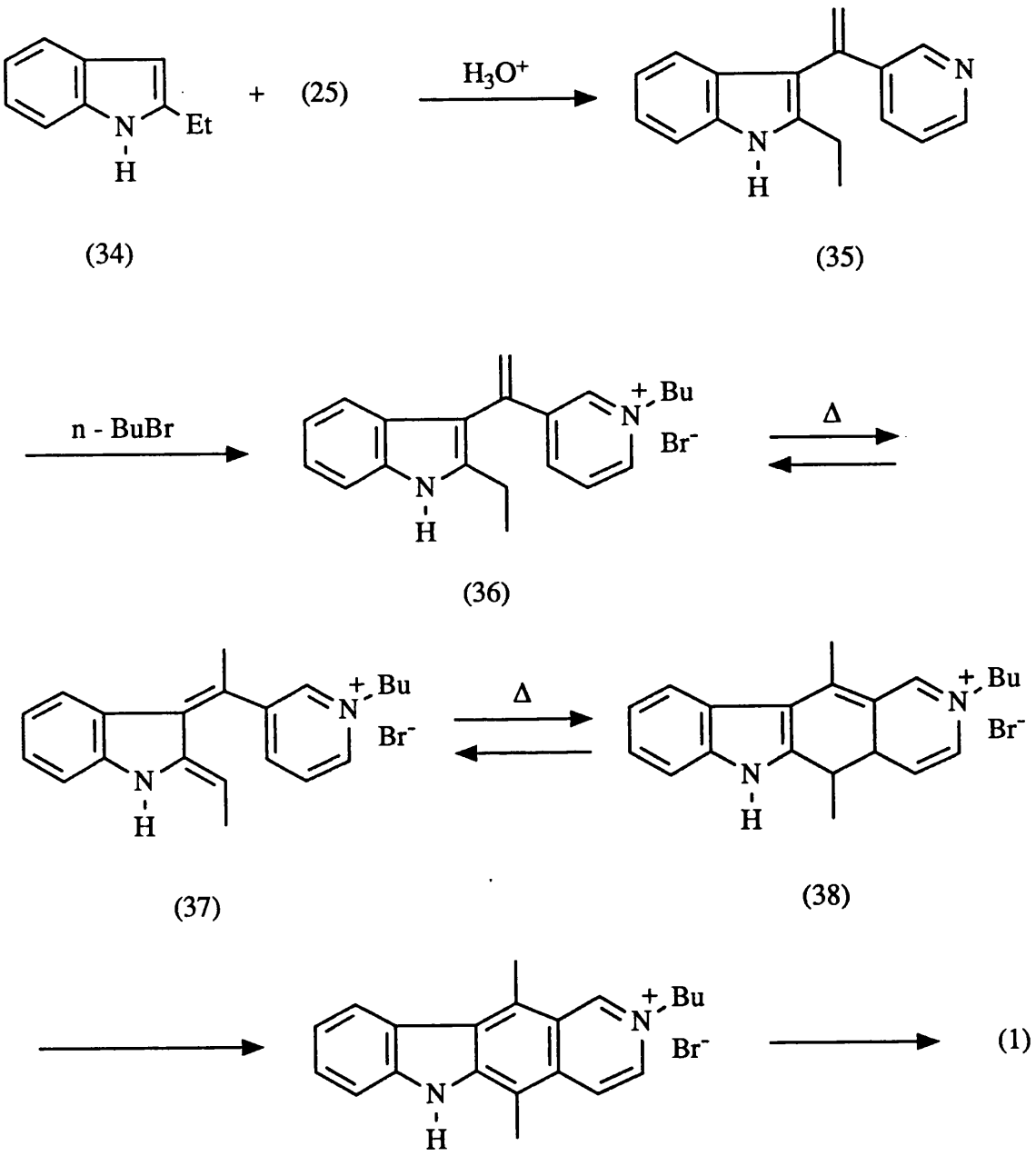
Thus employing the same reaction that Woodward had used, but using hydrogen chloride as catalyst, the adduct (25a) was obtained in 81% yield. Vacuum pyrolysis of this adduct (25a) produced the single indole species (30) in 50% yield. Catalytic hydrogenation of this species afforded the key intermediate (27) in 90% yield.

When the reductive acetylation of compound (27) was attempted, by reaction with acetic anhydride and zinc, the expected product (31) presumably reacts further, under the conditions employed, as 2-acetyl-1,2-dihydroellipticine (33) was isolated in 48% yield. This product (33) was hydrolysed and aromatised by heating with 10% aqueous sulphuric acid in refluxing methanol and bubbling with air, to afford ellipticine (1) in 68% yield.

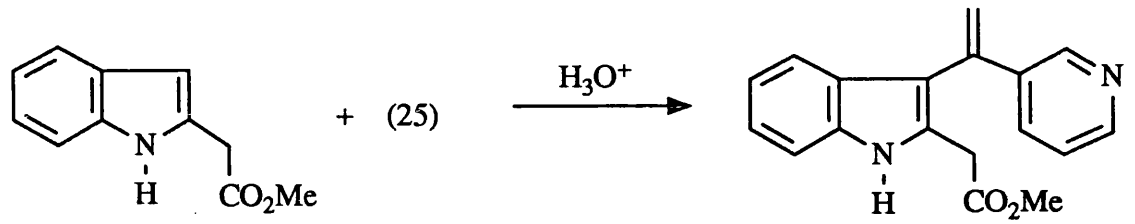
Another example of this approach was reported by Bergman and Carlsson.[41] Here, a vinyl indole (35) is prepared by the condensation of 2-ethylindole (34) and 3-acetylpyridine (25). After quaternisation with n-butyl bromide the intermediate (36) is heated at 500-600°C to afford ellipticine in 72% yield. (Scheme 13). The quaternary salt (36) presumably undergoes thermal isomerisation to the triene (37) prior to cyclisation to the intermediate (38), which, under the severe conditions employed loses hydrogen bromide and butane to yield ellipticine (1).

Weller and Ford[42] have developed this methodology to give a less severe route to ellipticine (1). (Scheme 14).

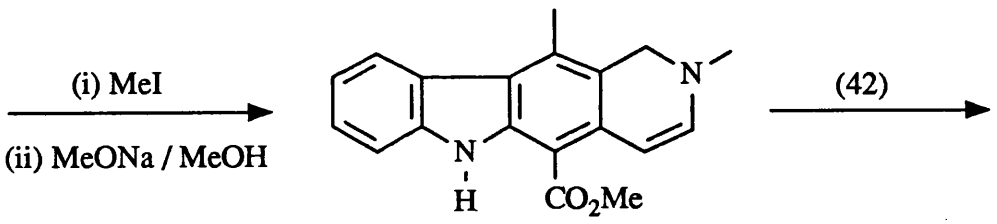
Thus, condensation of 2-methoxycarbonylmethylindole (39) with 3-acetylpyridine (25), under conditions first used by Bergman[41], gave the adduct (40) (81%). Methylation and immediate exposure of the resulting pyridinium salt to methoxide generated the labile dihydropyridine (41) (62%), which on direct treatment with the oxidising agent 3-ethyl-nicotinate-methiodide (42) gave the quaternised salt (43) (78%). Reduction of the product (43) with sodium bis-(2-methoxyethoxy)aluminium hydride (RED-AL), followed by oxidation with (42), furnished N-2-methylellipticinium iodide (44) (85%). Demethylation of (44) with sodium thiophenoxide gave ellipticine (1) (91%).



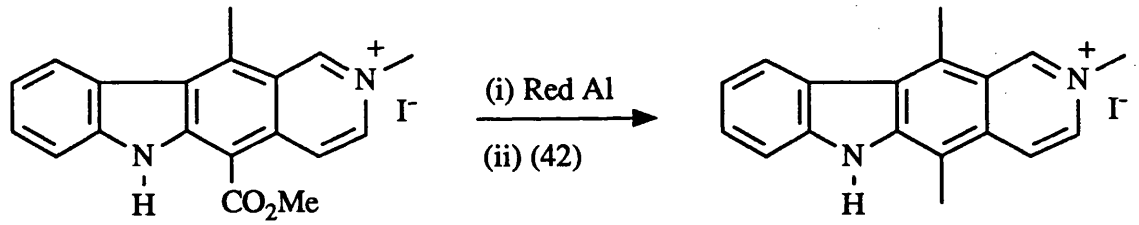
Scheme 13



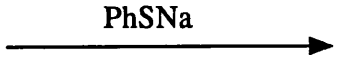
(39) (40)



(41)



(43) (44)

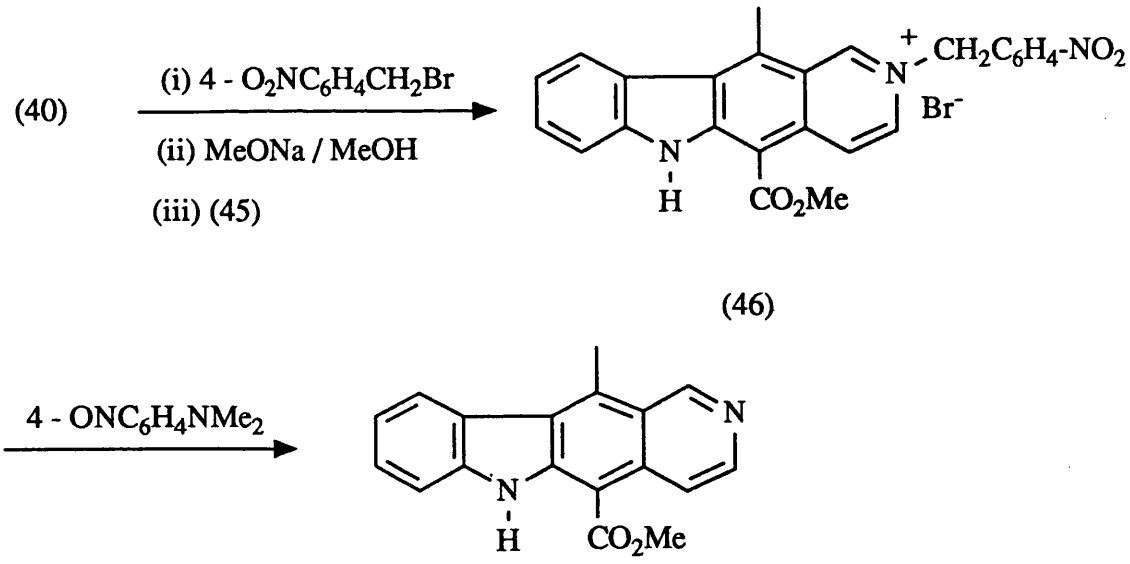


(1)

Scheme 14

Isolation of Weller's pyridium salt (43) would give a useful intermediate for 5-substituted ellipticines. However, Archer[43] attempted the demethylation of the salt (43) using sodium thiophenoxide but found the conditions too drastic to prevent the methoxycarbonyl group surviving unchanged.

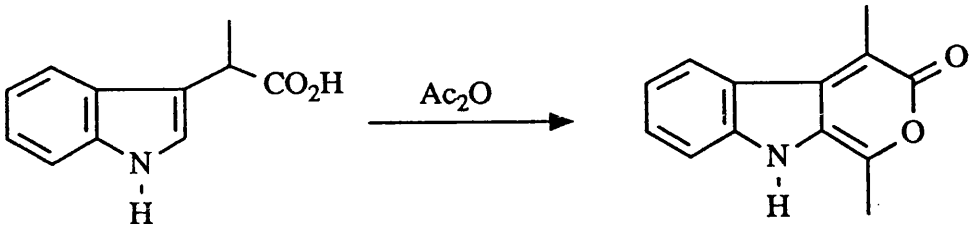
This problem was circumvented by quaternising the adduct (40) with 4-nitrobenzyl bromide (Scheme 15). Treatment of this quaternary salt with sodium methoxide followed by oxidation with 3-ethyl-nicotinate-methiobromide (45) furnished the salt (46) (80%). This salt was found to undergo debenzylation on treatment with 4-nitroso-N,N-dimethylaniline to afford the ester (47) (47%). Archer *et al.*[25] have utilised this compound (47) to derive various 5-substituted analogues of ellipticine.



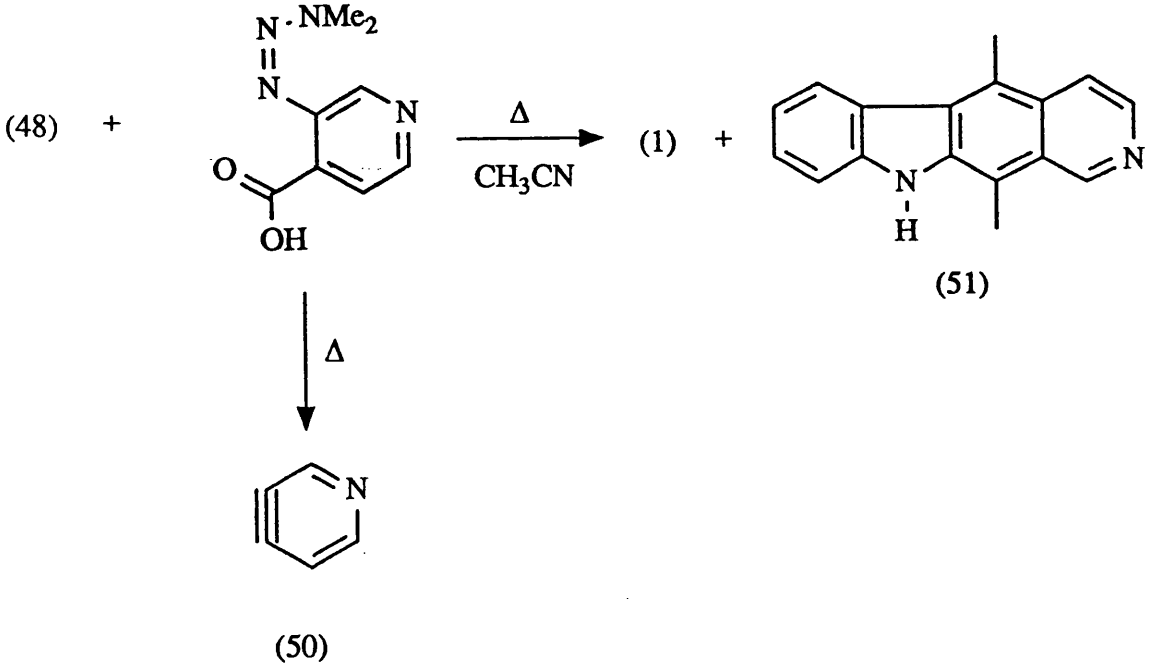
Scheme 15

Moody *et al.*[44] have developed a new concise synthesis of ellipticine by utilising a Diels-Alder reaction. The prerequisite diene, 1,4-dimethylpyrano[3,4-*b*]indol-3-one (48), was prepared in 44% yield by the reaction of α-methylindole-3-acetic acid with acetic anhydride in the presence of boron trifluoroetherate. A Diels-Alder reaction of the diene (48)

with 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid (49), a precursor of 3,4-pyridyne (50), gave ellipticine (1) (20%) together with an equal amount of isoellipticine (51). (Scheme 16).



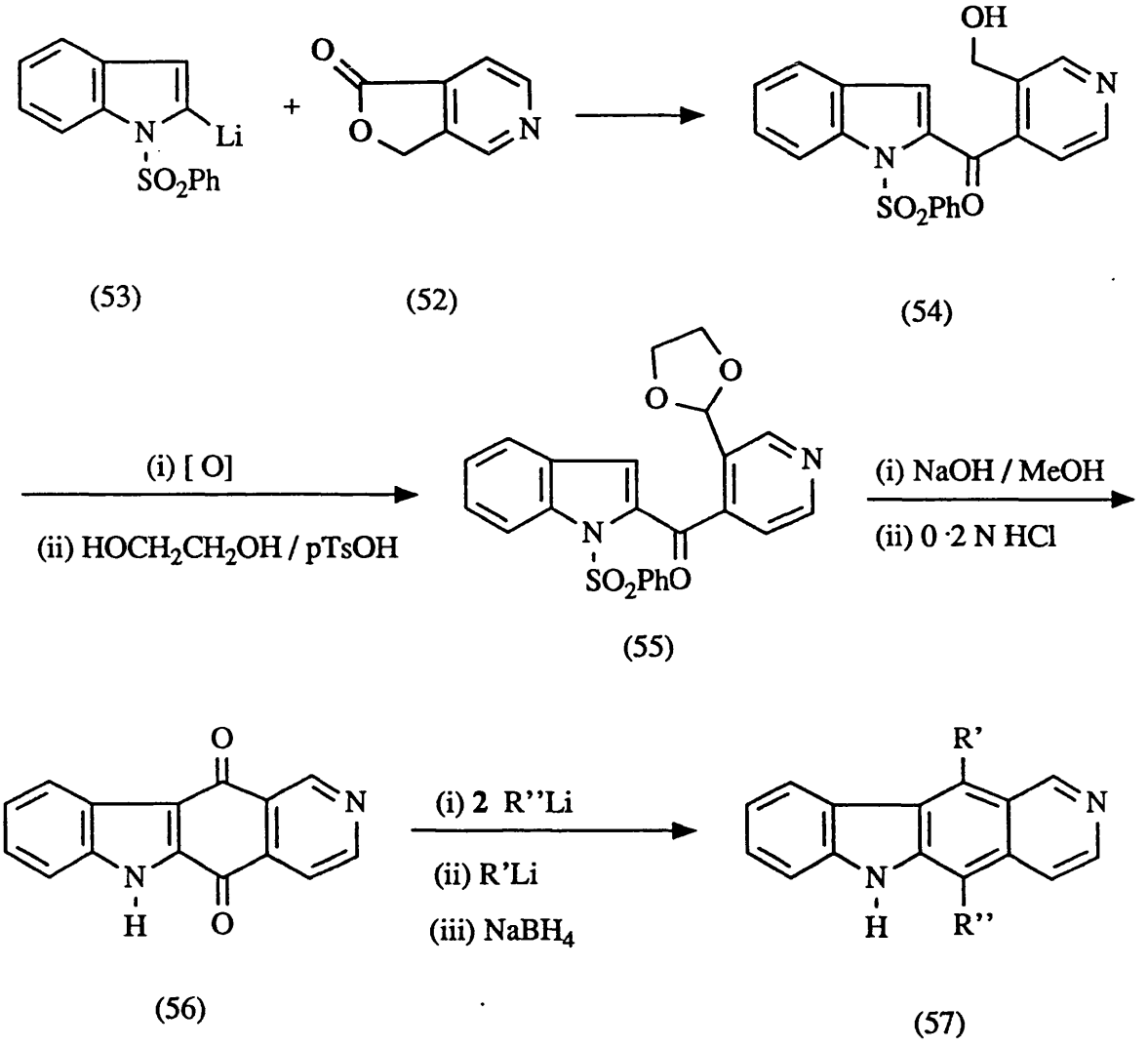
(48)



(50)

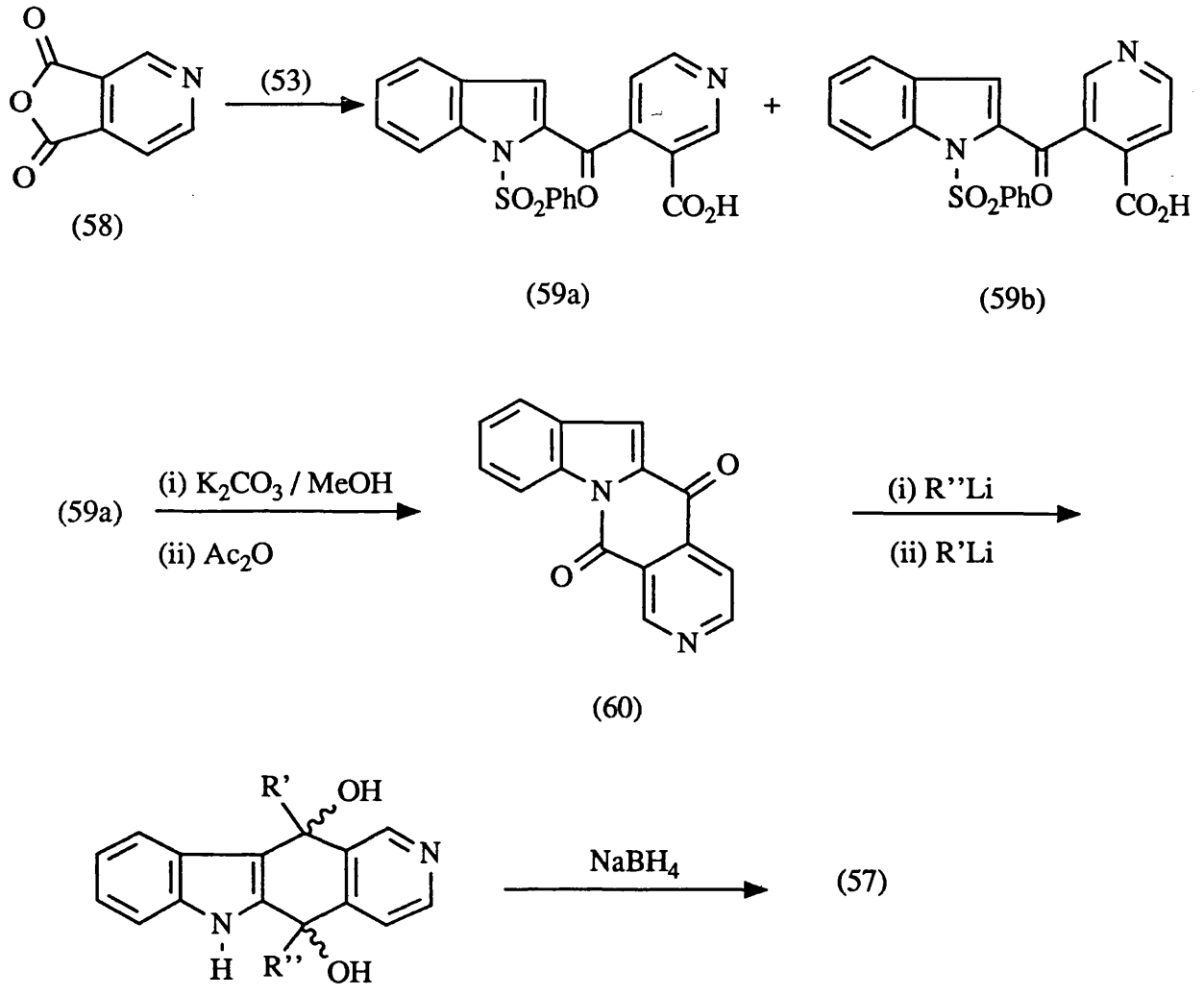
Scheme 16

Joule *et al.*[45] have developed a versatile quinone intermediate (56) which allows selective functionalisation at the 5- and 11- position of ellipticines.(The intermediate (56) was first synthesised by Snieckus *et al.*[46]). Joule[45] has shown that the pyridolactone (52) reacts with 2-lithio-1-benzenesulphonylindole (53) to afford the hydroxylketone (54). This was then oxidised to afford the ketoaldehyde, which as the acetal (55) , was N-deprotected and cyclised to the quinone (56), by treatment with hydrochloric acid in the presence of air. (Scheme 17).


Li
SO_2Ph
O
O
N
OH
N
N
SO_2PhO
(53)
(52)
(54)
(i) [O]
(ii) $HOCH_2CH_2OH$ / pTsOH
O
O
N
N
SO_2PhO
(55)
(i) NaOH / MeOH
(ii) 0 ·2 N HCl
O
N
N
H
O
(i) 2 R''Li
(ii) R'Li
(iii) $NaBH_4$
R'
N
N
H
R''
(56)
(57)

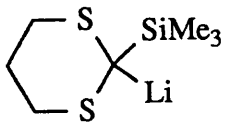
Scheme 17

A similar approach has been developed by Gribble *et al.*[47] (Scheme 18).



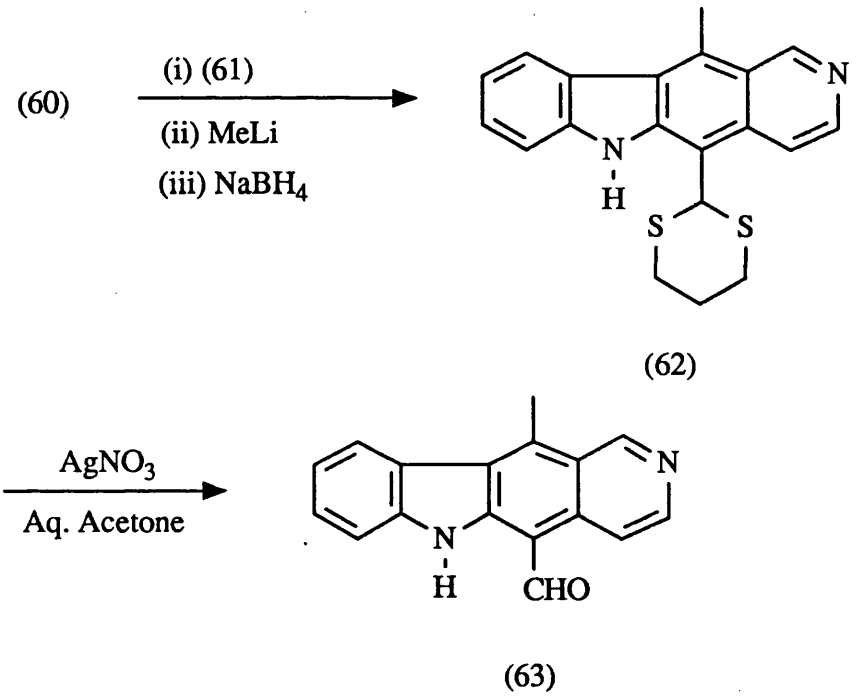
Scheme 18

Thus, reaction of 2-lithio-1-benzenesulphonylindole (53) with cinchomeronic anhydride (58) affords a mixture of keto acids (59a) and (59b). (92:8, 78%). The major isomer (59a), on hydrolysis with potassium carbonate-methanol, followed by treatment with hot acetic anhydride furnished the keto lactam (60). This compound (60) again proves to be a key intermediate for the selective functionalisation of 5- and 11- substituted ellipticines (57).



(61)

The use of 2-lithio-2-trimethylsilyl-1,3-dithiane (61) as a formyl anion synthetic equivalent led to the first total synthesis of the naturally occurring 5-formyl-11-methyl-6H-pyrido[4,3-*b*]carbazole (63)[48] (Scheme 19).

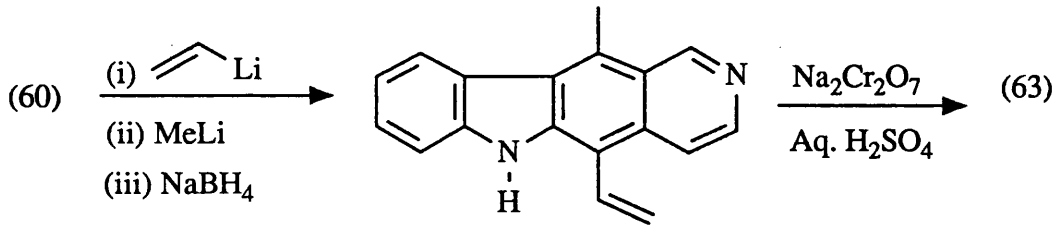


Scheme 19

Thus, stepwise treatment of the keto lactam (60) with (61), methyllithium and then sodium borohydride gave 5-(1,3-dithian-2-yl)-11-methyl-6H-pyrido[4,3-*b*]carbazole (62)

(25%). Cleavage of the dithianyl function with aqueous silver nitrate gave the aldehyde (63) (100%).

The synthesis of the aldehyde (63) has been improved by Gribble[55] by a variation on the same methodology. (Scheme 19a).



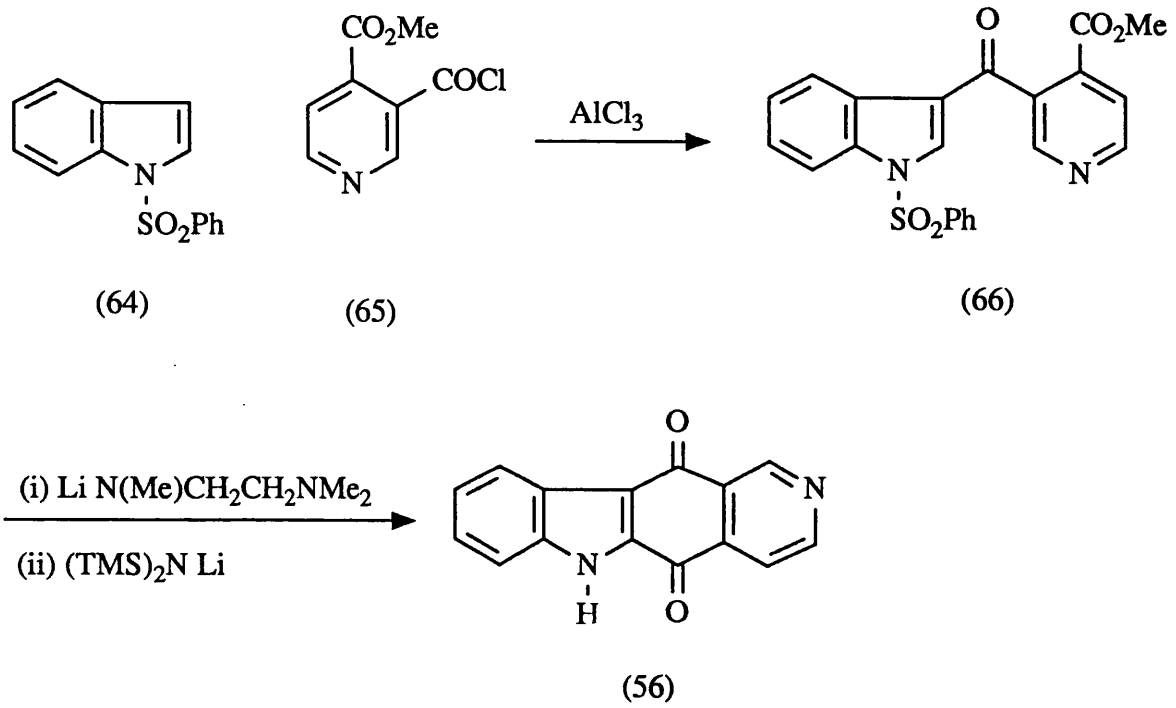
(74)

Scheme 19a

Thus, treatment of the intermediate (60) with vinyllithium, followed by methyllithium and reduction with sodium borohydride afforded the vinyl compound (74) in 78% yield. Oxidation with chromic acid in the presence of a dispersing agent furnished the required aldehyde (63) (74%).

This alkaloid (63) was first isolated and characterised by Koch *et al*[49] from the African tree *Strychnos dinklagei.* Since its discovery and synthesis, the alkaloid has been isolated as a metabolite during the incubation of ellipticine (1) will cell cultures of several *Choisya ternata* strains.[50]

Gribble *et al*[51] have formulated another new synthesis of the key intermediate quinone (56) by applying a similar acylation reaction, but with an acid chloride (65). (Scheme 20). A base induced cyclisation reaction of the resulting keto ester (66) yielded the quinone (56) (24% overall), which has previously been converted to ellipticine and several derivatives. (Scheme 17).

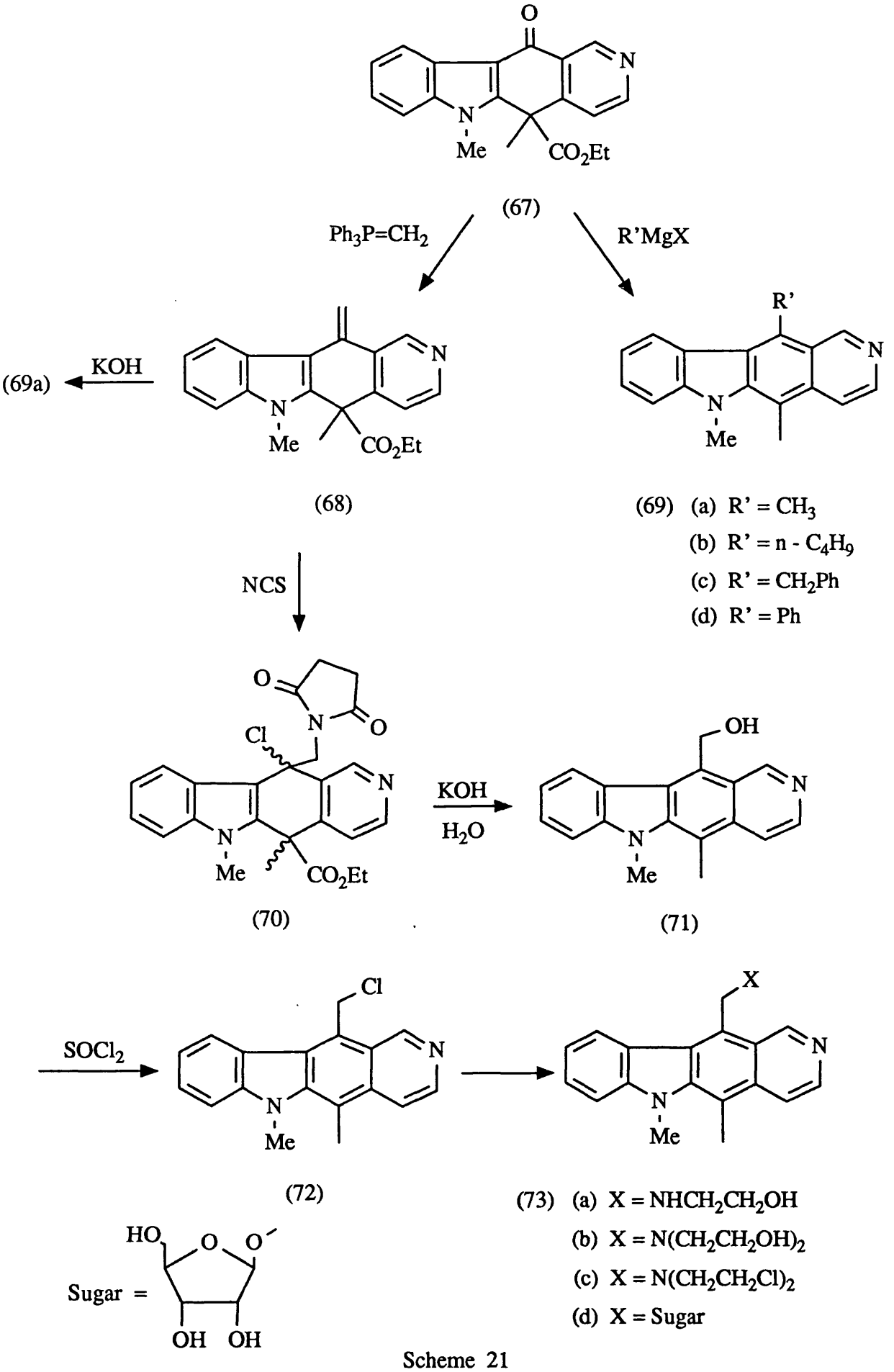


Scheme 20

The cyclisation step was most efficiently achieved using the anion derived from N,N,N'-trimethylethylenediamine, followed by treatment with lithium bis(trimethysilyl)amide.

In recent years, attention has been focussed on the introduction of more elaborate groups into the C ring in order to improve the therapeutic index of the ellipticines. A illustration is provided by Pandit *et al.*[52] By exploiting the presence of an 11-keto group in the previously synthesised intermediate (67).[53,54] (prepared in six steps from N-methyl-indole), they have prepared a large number of 6-methylellipticine derivatives, [(69a-d) and (73a-d)] (Scheme 21).

Reaction of the keto ester (67) with an excess of a Grignard reagent (CH_3MgI, BuMgI, $PhCH_2MgI$ or PhMgI) afforded the 6-methyl-11-substituted ellipticine derivatives (69a-d). 6-Methylellipticine (59a) was also obtained by the reaction of (67) with methylenetriphenyl phosphorane, followed by hydrolytic decarboxylation of the resulting intermediate (68).


(67)
Ph3P=CH2
R'MgX
KOH
(69a)
(68)
(69) (a) R' = CH3
(b) R' = n - C4H9
(c) R' = CH2Ph
(d) R' = Ph
NCS
KOH
H2O
(70)
(71)
SOCl2
(72)
(73) (a) X = NHCH2CH2OH
(b) X = N(CH2CH2OH)2
(c) X = N(CH2CH2Cl)2
(d) X = Sugar
Sugar =

Scheme 21

Furthermore, treatment of the intermediate (68) with N-chlorosuccinimide, followed by hydrolytic decarboxylation furnished the alcohol (71) (45%) which on reaction with thionyl chloride gave the chloro derivative (72) (100%).

The displacement of chloride with various nucleophiles (substituted amines or sugars) furnished various 11-substituted-6-methylellipticine derivatives (73a-d) (Scheme 21).

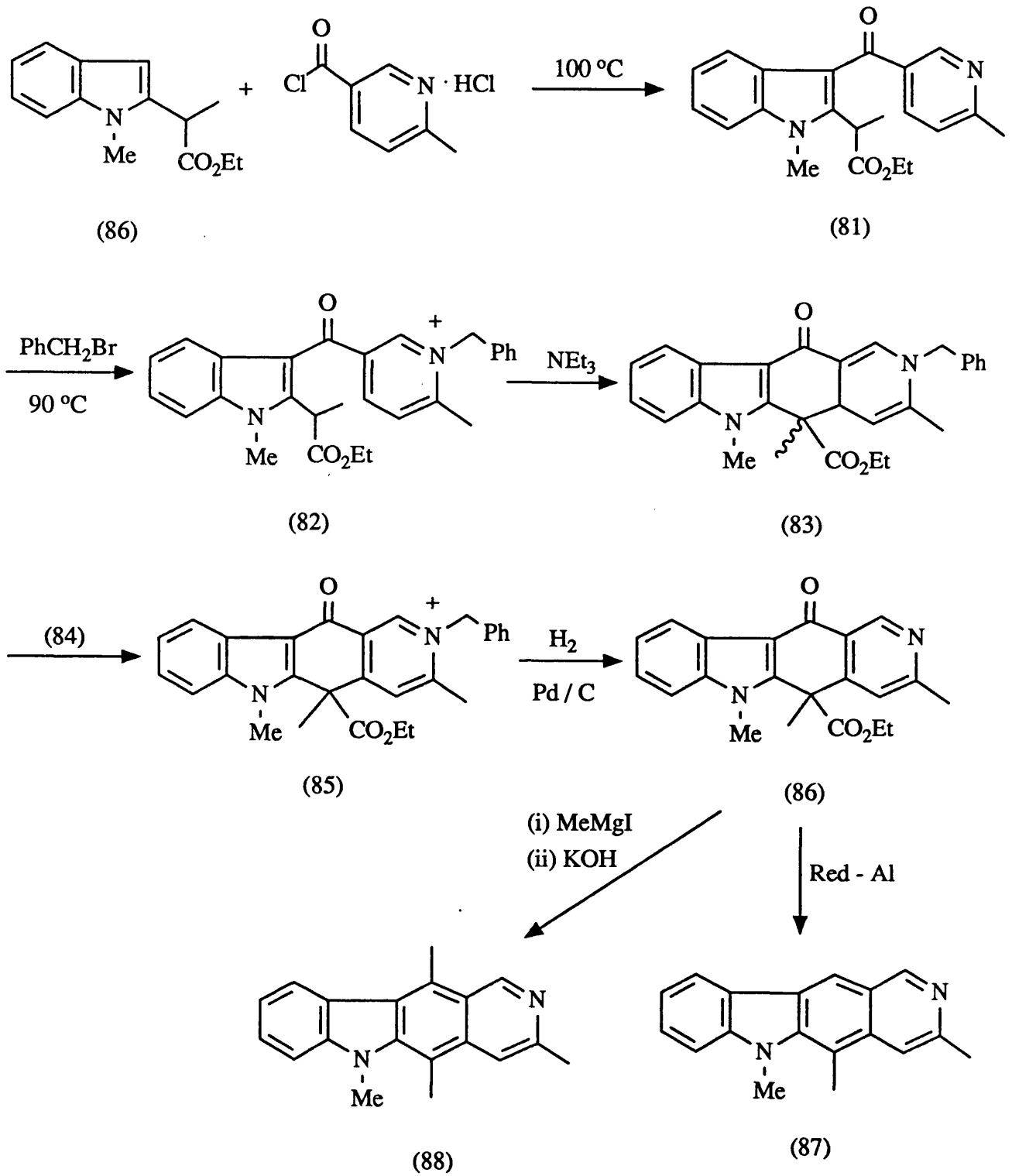
Pandit *et al*[57] have further developed this methodology for the synthesis of ring D modified 6-methylellipticine and 6-methylolivacine (Scheme 22).

Thus, acylation of the indole moiety of synthon (86), by 6-methylnicotinoyl chloride hydrochloride in sulfolane, afforded the ketone (81) (74%). Formation of the pyridocarbazole skeleton was then completed by N-benzylation and subsequent base-catalysed cyclisation of the resulting salt (82), which was not isolated. The product (83) was oxidised by N-benzylacridinium bromide (84) to yield the salt (85) (95%) which was then reductively debenzylated to yield the keto ester (86) (41%).

Reduction of (86) with Red-Al gave 3,5,6 trimethyl-6H-pyrido[4,3-*b*]carbazole (87) (39%). Conversion of (86) to 3,6-dimethylellipticine (88) was achieved in one practical step by reaction with an excess of MeMgI, followed by basic elimination.

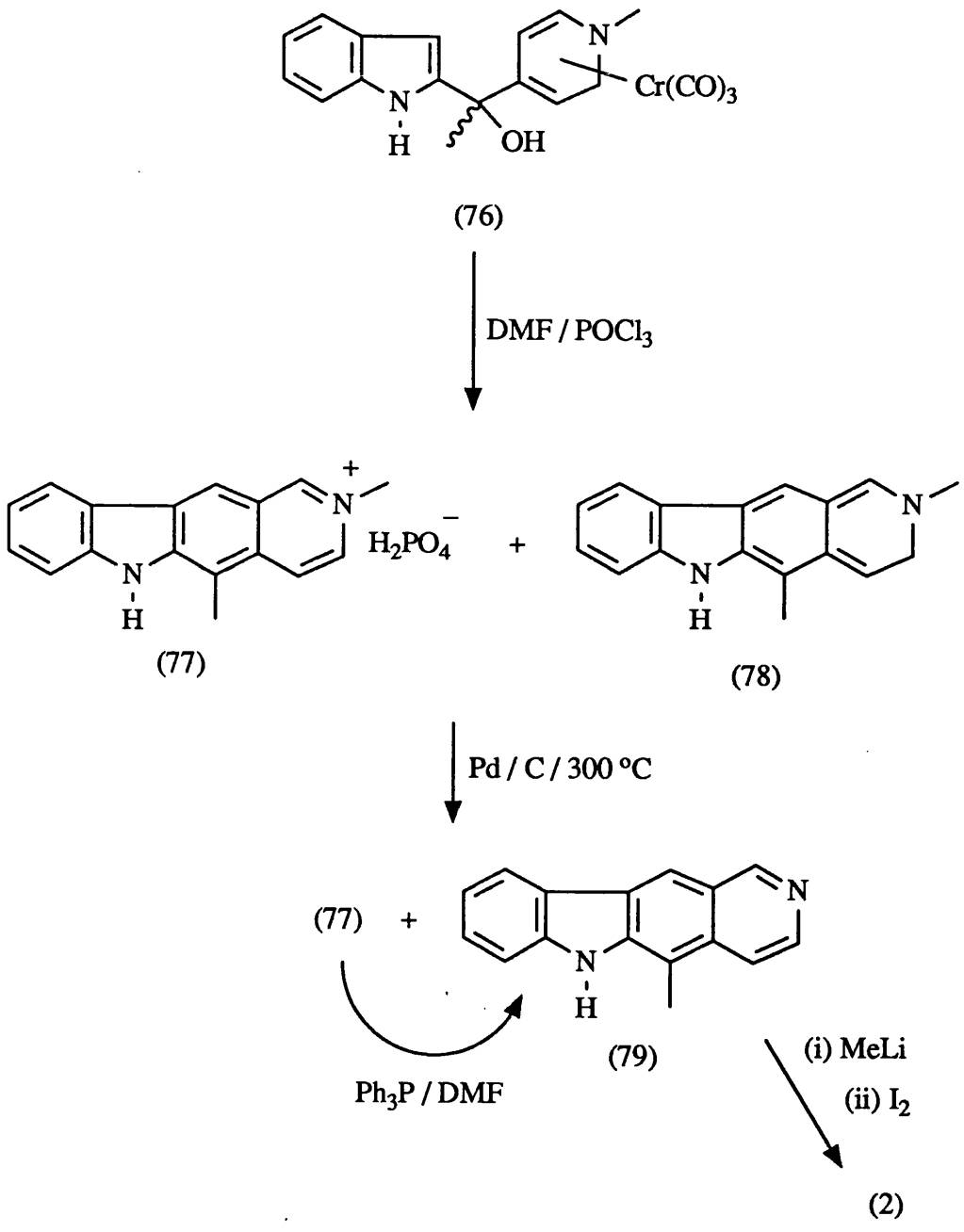
Kutney *et al*[56] have described a synthesis of olivacine (2) where the crucial step in the synthetic sequence utilises a tricarbonylchromium (0) complex of a suitable dihydropyridine (Scheme 23). Reaction of the complex (76) with the Vilsmeier reagent, prepared from DMF andphosphorusoxychloride resulted in a mixture of products (77) and (78). Hydrogenation of this mixture afforded a mixture of unconverted (77) and the pyridocarbazole (79). The former was demethylated to (79) by treating with triphenylphosphine in DMF.

Alkylation of the pyridocarbazole (79) with methyllithium followed by oxidation



(86) (81) (82) (83) (85) (86) (88) (87)

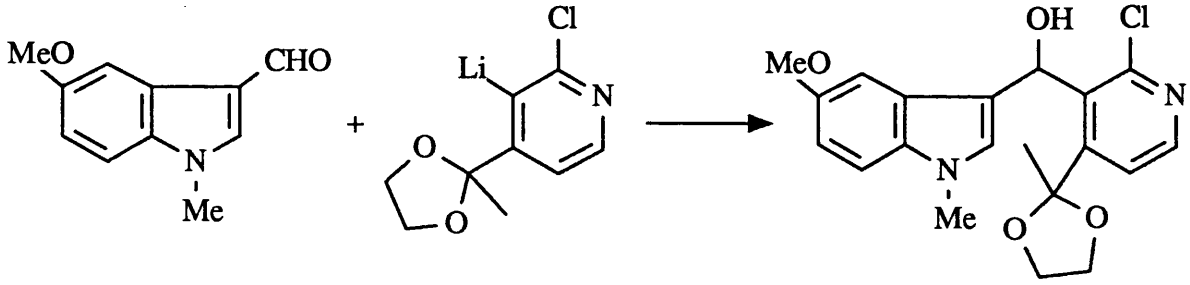
Scheme 22


N
Cr(CO)3
N
H
OH
(76)
DMF / POCl3
+
N
H2PO4
−
N
H
(77)
+
N
N
H
(78)
Pd / C / 300 °C
(77) +
N
N
H
(79)
Ph3P / DMF
(i) MeLi
(ii) I2
(2)

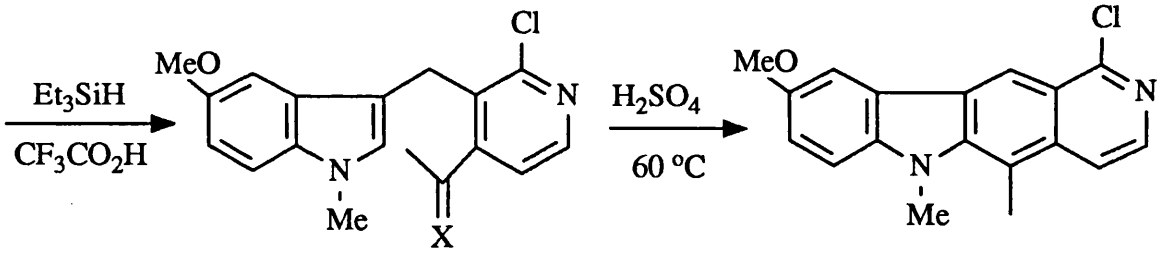
Scheme 23

with iodine afforded olivacine (2) (54%).

The remarkable antitumour properties of compounds (89) and (90)[58,59] prompted Bisagni *et al*[60] to develop a convergent synthesis to the 1-substituted ellipticine skeleton. (Scheme 24).



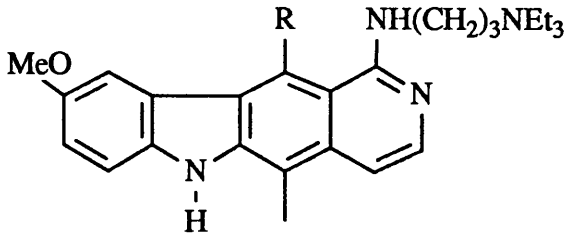
(91) (92) (93)



(94) X = OCH_2CH_2O
(94a) X = O

(95)

Scheme 24



(89) R = CH_3
(90) R = H

Thus, reaction of 3-formyl-5-methoxy-1-methylindole (91) with the 3-lithio derivative of 4-acetyl-2-chloropyridine ethylene glycol ketal (92)[61] furnished the alcohol (93) (65%).

Reduction of the alcohol (93) was performed in triethylsilane-trifluoroacetic acid medium. This procedure, however, yielded a complex mixture due to partial hydrolysis of the ketal (94) into the ketone (94a), followed by spontaneous acid catalysed cyclisation, resulting in traces of the required tetracyclic derivative (95). For this transformation to go to completion, the crude mixture was treated with 50% sulphuric acid at 60°C to afford 1-chloro-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-*b*]carbazole (95) (54%).

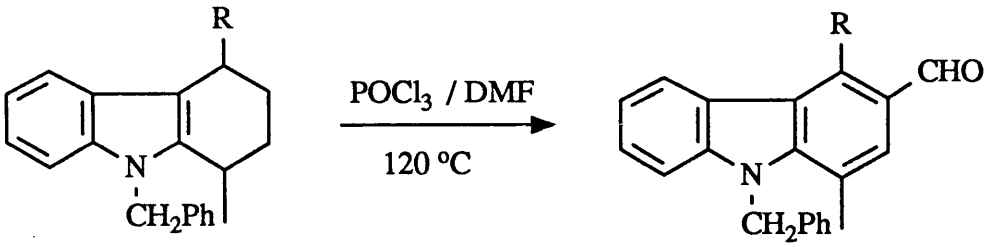
From this intermediate (95), six further amino derivatives have been synthesised by Paoletti and Bisagni.[76]

D-Type Syntheses

No new examples of this class of synthesis has appeared recently. The reaction sequences are essentially the same as described in the modified[62,63] Cranwell and Saxton[64] synthesis. New efforts, however, are being made to synthesise suitably functionalised carbazoles on which ring D can be elaborated.

Murakami *et al.*[66] have synthesisedthe 3-formylcarbazoles (97a) (39%) and (97b) (45%), by carrying out a Vilsmeier-Haack reaction with substituted 1,2,3,4-tetrahydro-N-benzylcarbazoles (96). The carbazole (97a) was converted into ellipticine (1), in poor yield by adaption of the modified[62,63] Cranwell and Saxton[64] methodology and debenzylation. (Scheme 25).

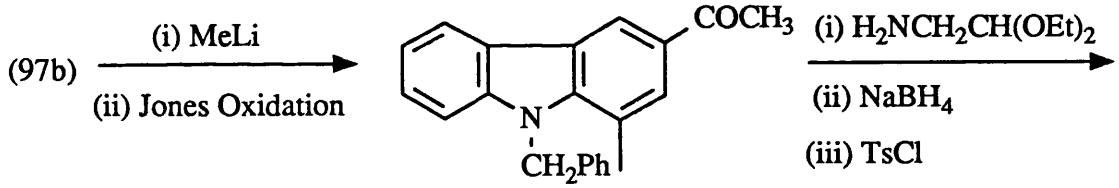
The aldehyde (97b) was converted into the ketone (98) by reaction with methyllithium, followed by oxidation. A similar sequence of reactions, as above, on the



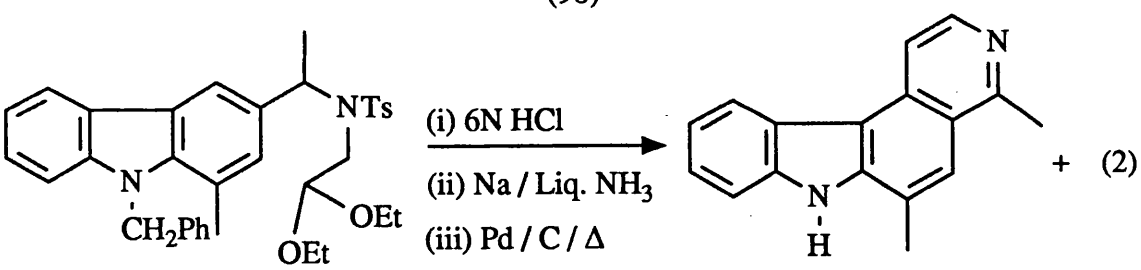
(96) (a) R = CH_3
(b) R = H

(97)

(97a) —(i) $H_2NCH_2CH(OEt)_2$ (ii) Li / Liq. NH_3 (iii) TsCl / $NaHCO_3$ (iv) 6N HCl→ (1)



(98)

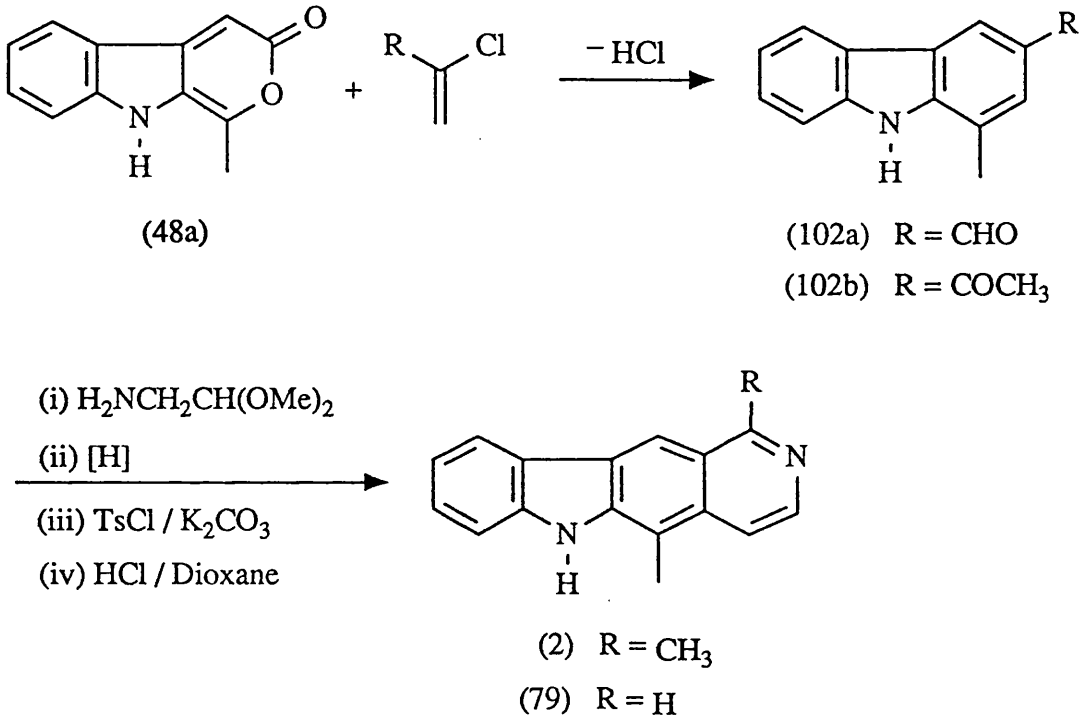


(99) (100)

Scheme 25

ketone (98) afforded a mixture of olivacine (2) (12%) and isoolivacine (100) (10%).

Narasimhan *et al.*[65] have developed a method to synthesise 3-formyl- and 3-acetylcarbazoles, using the cycloaddition reaction of 1-methylpyrano[3,4-*b*]indol-3-one **(48a)** with appropriately substituted haloalkenes, in high yield. The resulting carbazoles (102a) and (102b) have been converted to olivacine (2) and 11-desmethylellipticine (79) respectively, following the modified Cranwell and Saxton synthesis. (Scheme 26).



(48a)

(102a) R = CHO

(102b) R = $COCH_3$

(2) R = CH_3

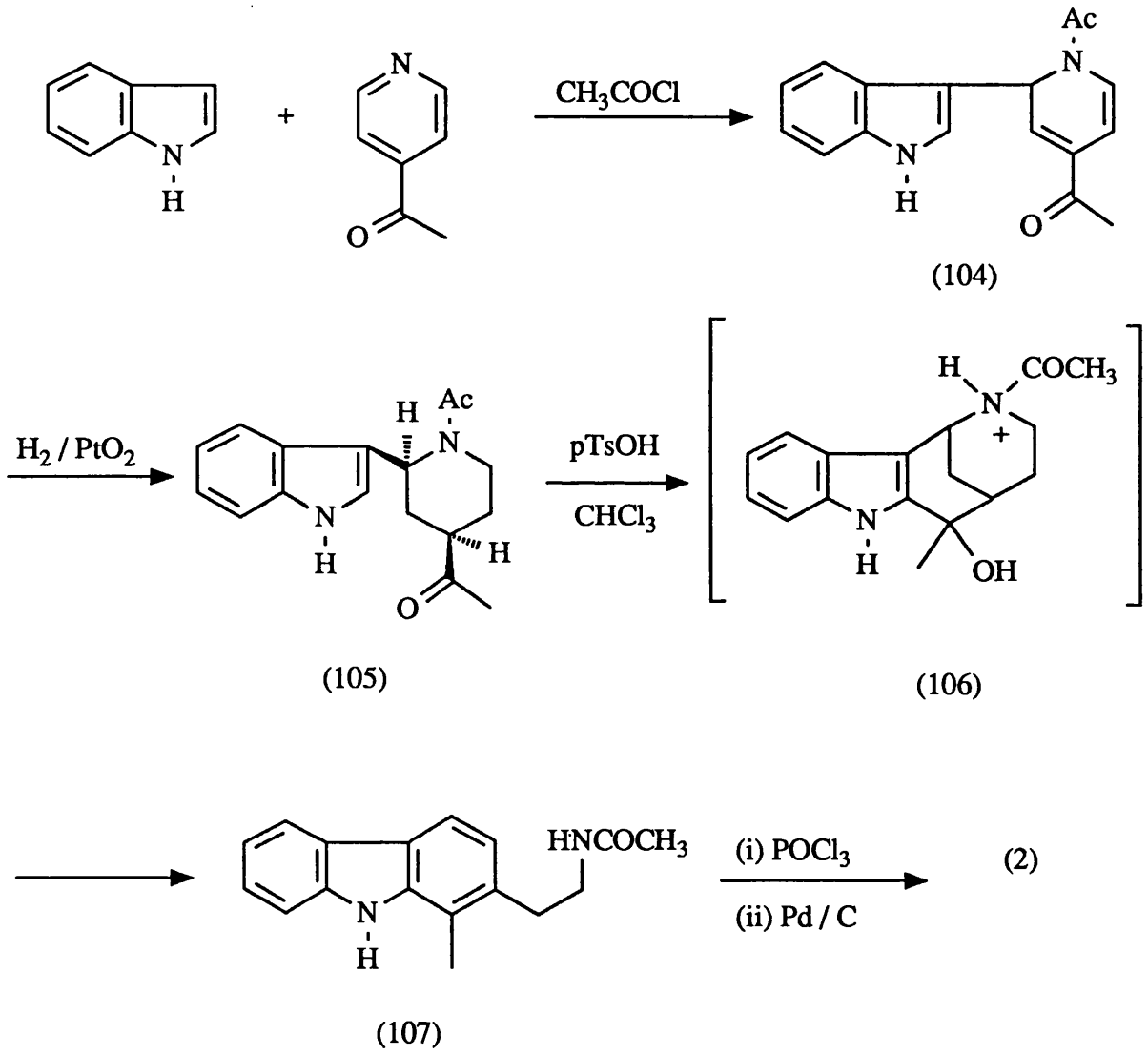
(79) R = H

Scheme 26

Ninomiya *et al.*[67] have developed a route to pyridocarbazoles by utilising a heteroarlation reaction between indole and 4-substituted pyridines (Scheme 27).

Thus, reaction of indole and 4-acetylpyridine in the presence of acetyl chloride, afforded the adduct (104) (39%). Catalytic dehydrogenation of this adduct (104) yielded the *cis*-piperidine (105).

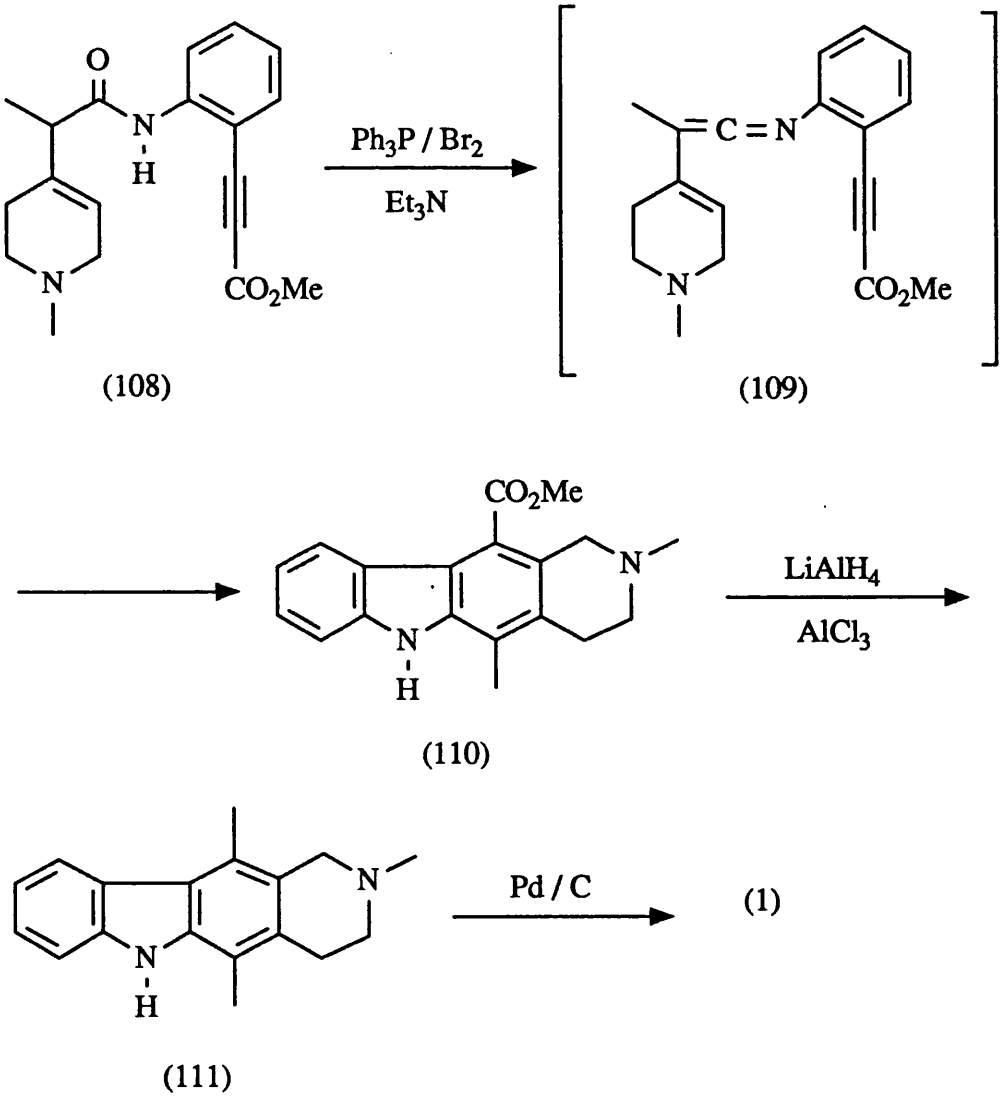
Treatment of this product with p-toluene sulphonic acid in chloroform afforded the carbazole (107) (62%), presumably *via* the intermediate (106), followed by spontaneous ring opening. The carbazole (107) was converted to olivacine (2) (40%) by a standard[68,69] Bischler-Napieralski cyclisation of the acetate (107), followed by catalytic dehydrogenation. (Scheme 27).



Scheme 27

B + C Type Synthesis

A new synthetic approach to ellipticine (1) has recently been reported by Differding and Ghosez[26]. This method involves simultaneous construction of the B + C ring, employing an intramolecular Diels-Alder cycloaddition of an acetylenic vinylketenimine as the key step. Heating the alkyne (108) with triphenylphosphine and bromine in the presence of triethylamine generates the vinylketenimine (109), *in situ*, which undergoes an intramolecular cycloaddition to afford the carbazole (110) (50%). Ellipticine (1) was obtained by mixed hydride reduction of the ester (110), followed by dehydrogenation - dealkylation of the carbazole (111). (Scheme 28).



(108) (109) (110) (111)

Scheme 28

Derivitisation of Ellipticine and its analogues

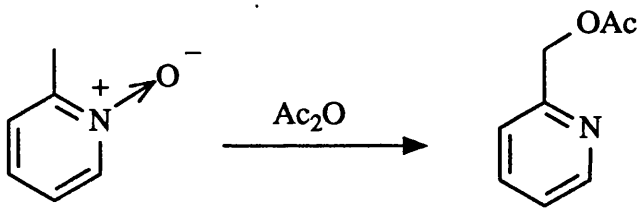
Bisagni *et al.*[70] have synthesised a number of 1-aminomethylpyrido[4,3-*b*]carbazole derivatives from 9-methoxyolivacine (112). (Scheme 29).

Thus, selenium dioxide oxidation of (112) gave 1-formyl-11-desmethylellipticine (113).

Condensation of this aldehyde with amines gave the corresponding imines (114a) (66%) and (114b) (66%). Reductive amination of the intermediate (113) gave the amines (115a) (67%) and (115b) (60%).

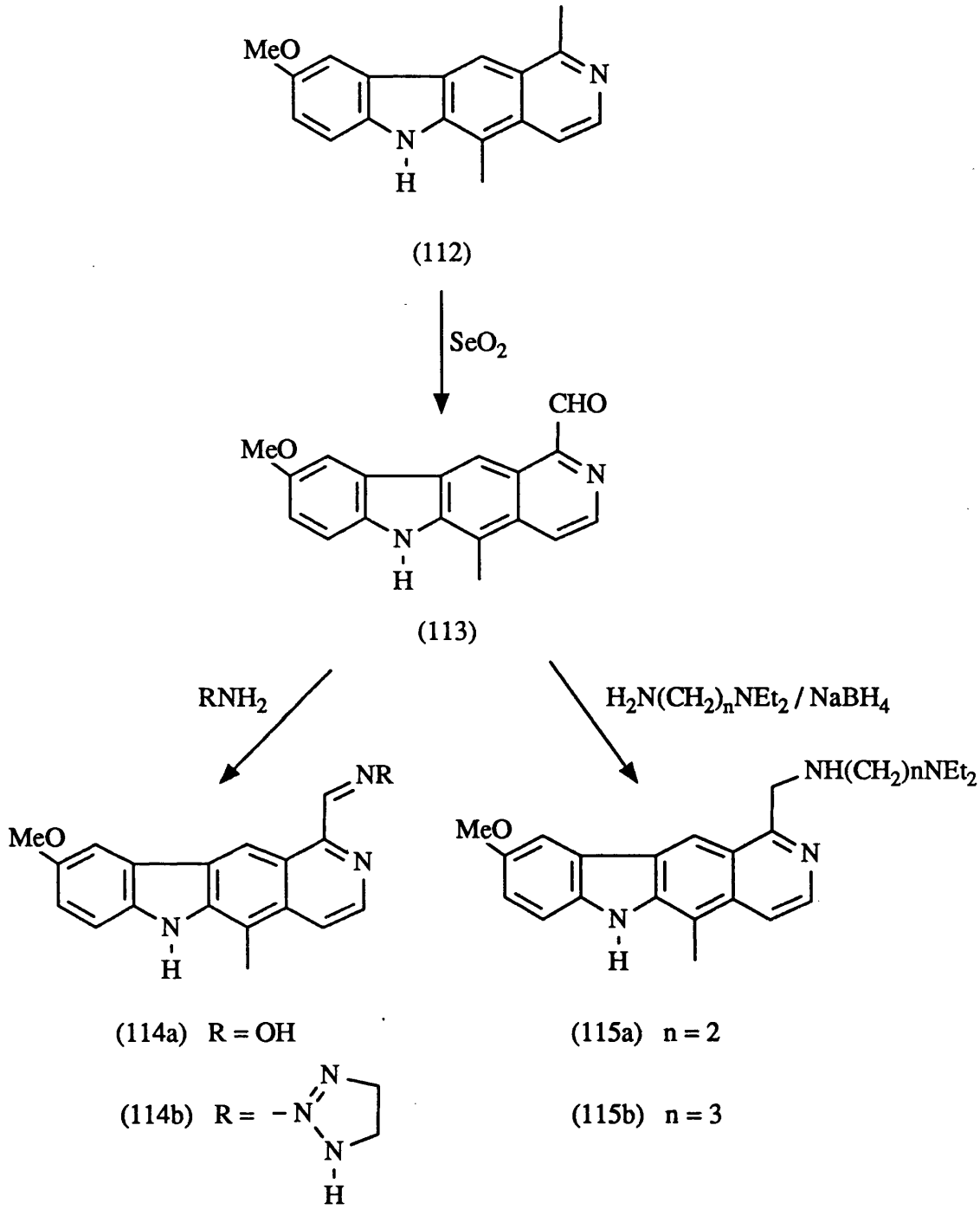
Pandit *et al.*[71] have developed a method for introducing functional substituents at the C_{11}-methyl group of 6-methylellipticine. Subsequently, they have utilised this approach for the synthesis of several sugar derivatives. (Scheme 33).

As the C_{11}-methyl ellipticine is conjugatively analogous to the methyl group of 2-methylpyridine, Pandit considered the possibility of applying the known chemistry[72] of pyridine-N-oxide to the pyridocarbazole system. (Scheme 30).



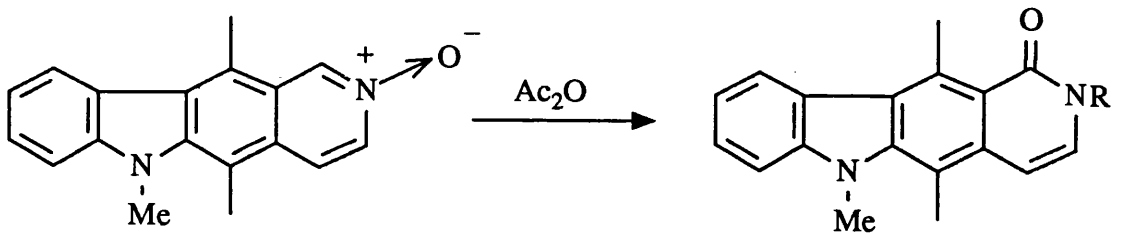
Scheme 30

However, when 6-methylellipticine-2-oxide (116) was treated with acetic anhydride, no substitution at C-11 was obtained. Two products were isolated and characterised as (117) and (118). (Scheme 31).


MeO
N
H
(112)
SeO2
CHO
MeO
N
H
(113)
RNH2
H2N(CH2)nNEt2 / NaBH4
NR
MeO
N
H
NH(CH2)nNEt2
MeO
N
H
(114a) R = OH
(114b) R =
(115a) n = 2
(115b) n = 3

Scheme 29

However, reacting 6-methylellipticine (119) with one equivalent of lithium diisopropylamide (LDA) and subsequent quenching with formaldehyde gave the hydroxymethylation product (120) in over 50% yield. (Scheme 32).

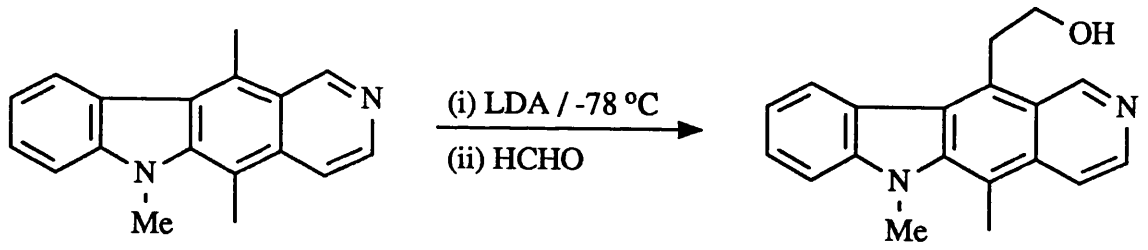


(116)

(117) R = H

(118) R = Ac

Scheme 31



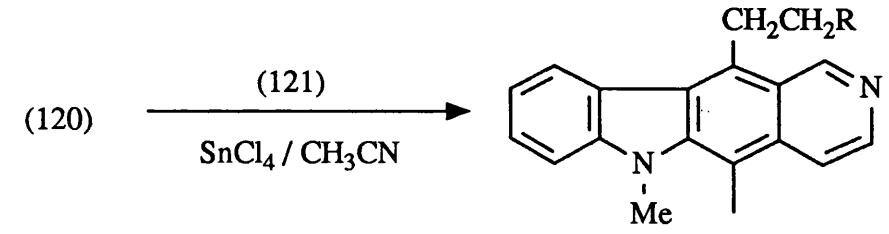
(119)

(120)

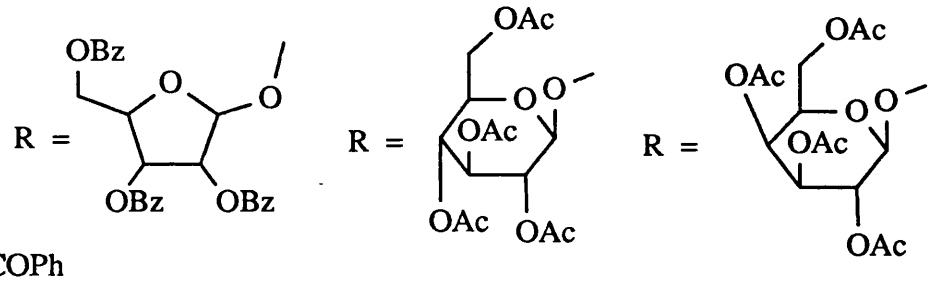
Scheme 32

The hydroxyl group in (120) provides a convenient function for coupling the ellipticine unit to diverse substrates and this was carried out by reaction of (120) with appropriately derivatised sugars (121) using tin tetrachloride as catalyst. (Scheme 33).

Apart from one report desribing the low yielding synthesis of 9-hydroxyellipticine (12) from ellipticine (1)[73], the introduction of a hydroxyl group at position 9 of the ellipticine skeleton has been achieved by utilisation of an appropriately protected hydroxylated aromatic starting material.



(122)

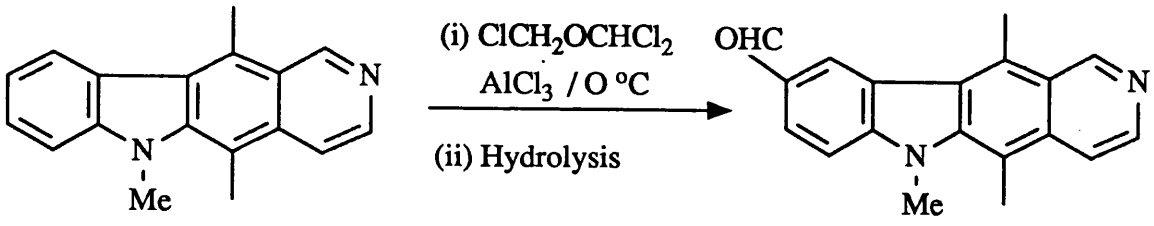


Bz = COPh

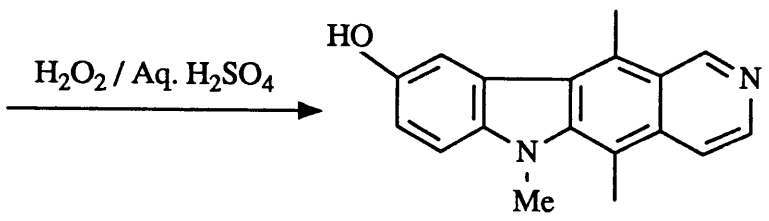
(122a) (122b) (122c)

Scheme 33

Pandit *et al.*[74], however, have recently developed a practical method for the introduction of a hydroxyl group at the C-9 position of 6-methylellipticine. This involves a reaction sequence which includes regioselective C-9 formylation, followed by a Baeyer-Villiger rearrangement (Scheme 34).



(123)



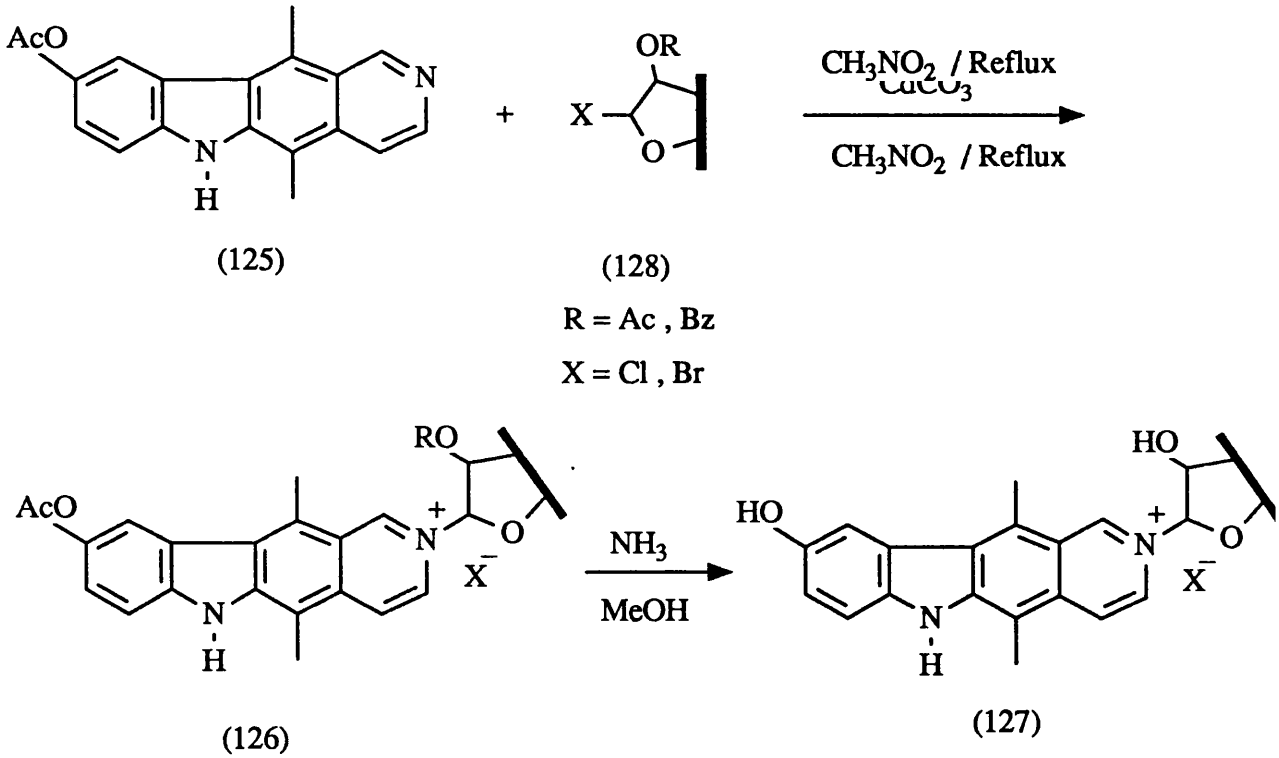
(124)

Scheme 34

However, it should be noted that the utility of all the methodologies developed by Pandit[52,57,71,74] depend greatly on the success of removing the 6-methyl group as 6-substituted ellipticines are not effective anticancer agents.[133]

In an attempt to improve the solubility of ellipticine derivatives, Honda *et al.*[75] have reported the synthesis of a number of 9-hydroxyellipticine-2-glycosides (127) for pharmacological evaluation. 9-Acetoxyellipticine glycosides (126) were stereoselectively prepared by heating 9-acetoxyellipticine (125) and the appropriately peracylated glycosyl halide (128) with cadmium carbonate in refluxing nitromethane.

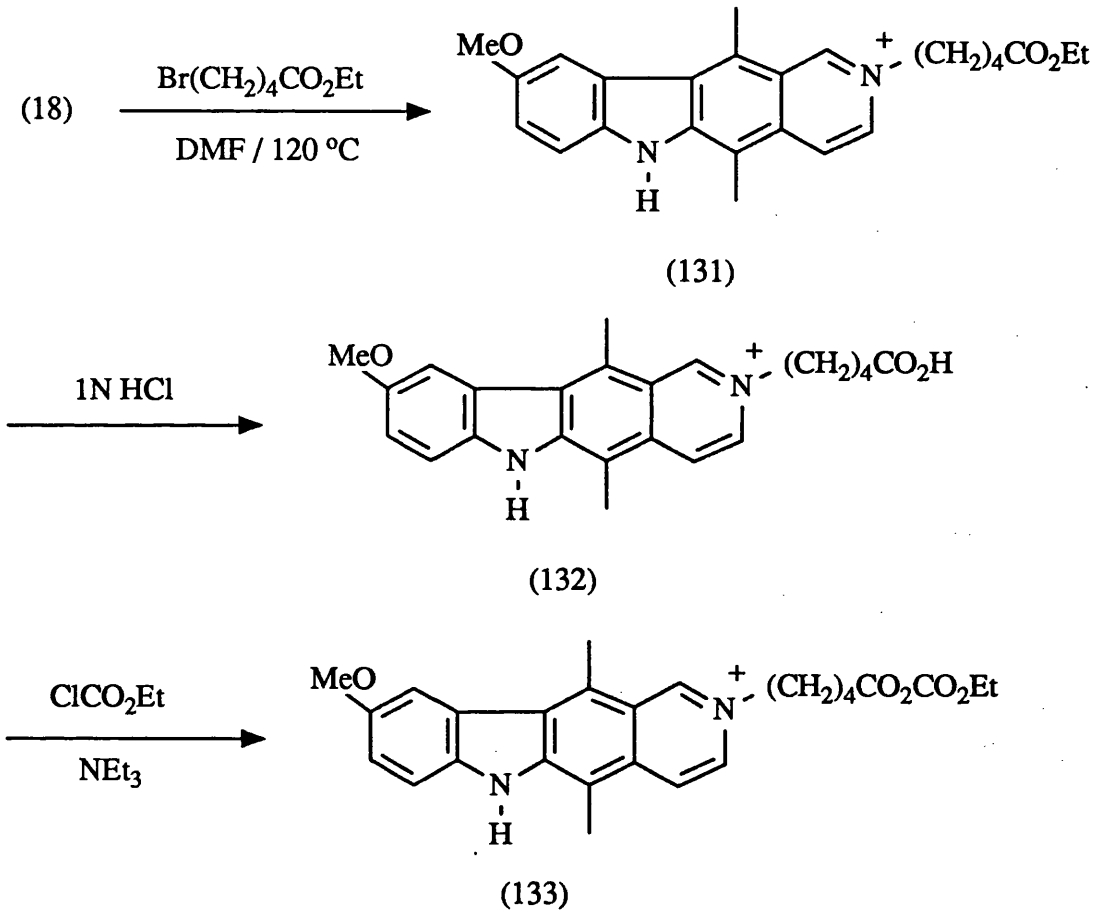
Deprotection was achieved with methanolic ammonia to give the desired 9-hydroxyellipticine glycosides (127). (Scheme 35).



Scheme 35

Meunier *et al.*[77] have recently reported the synthesis of manganese-, iron-and zinc-porphyrins linked to 9-methoxyellipticine (18) as potential DNA cleavers.

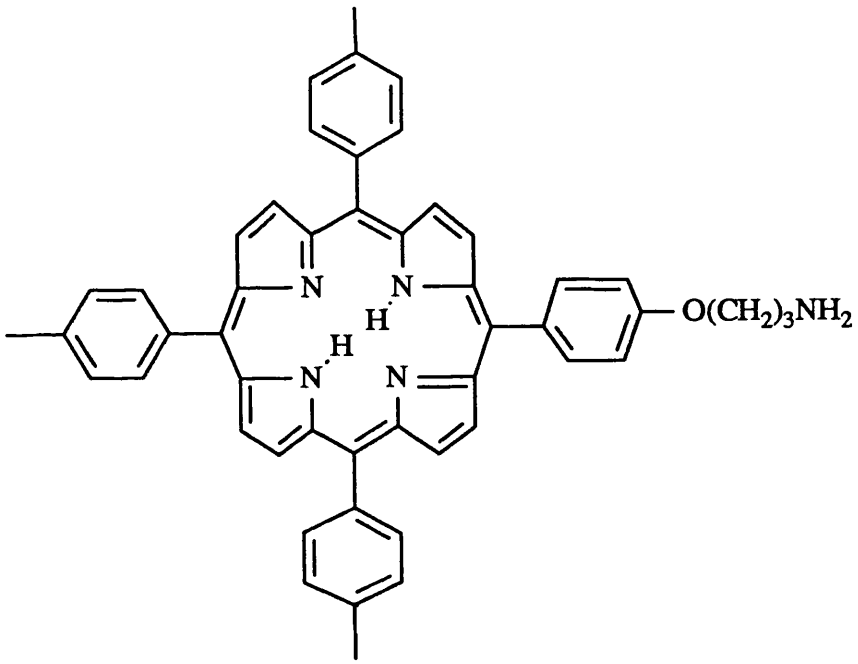
Alkylation at the 2-position of 9-methoxyellipticine (18) with ethyl 5-bromovalerate yielded the salt (131) (87%), which was saponified with dilute hydrochloric acid to quantitatively afford the free acid (132). The mixed anhydride (133) was generated by treatment of the acid (132) with ethylchloroformate in the presence of triethylamine. (Scheme 36).



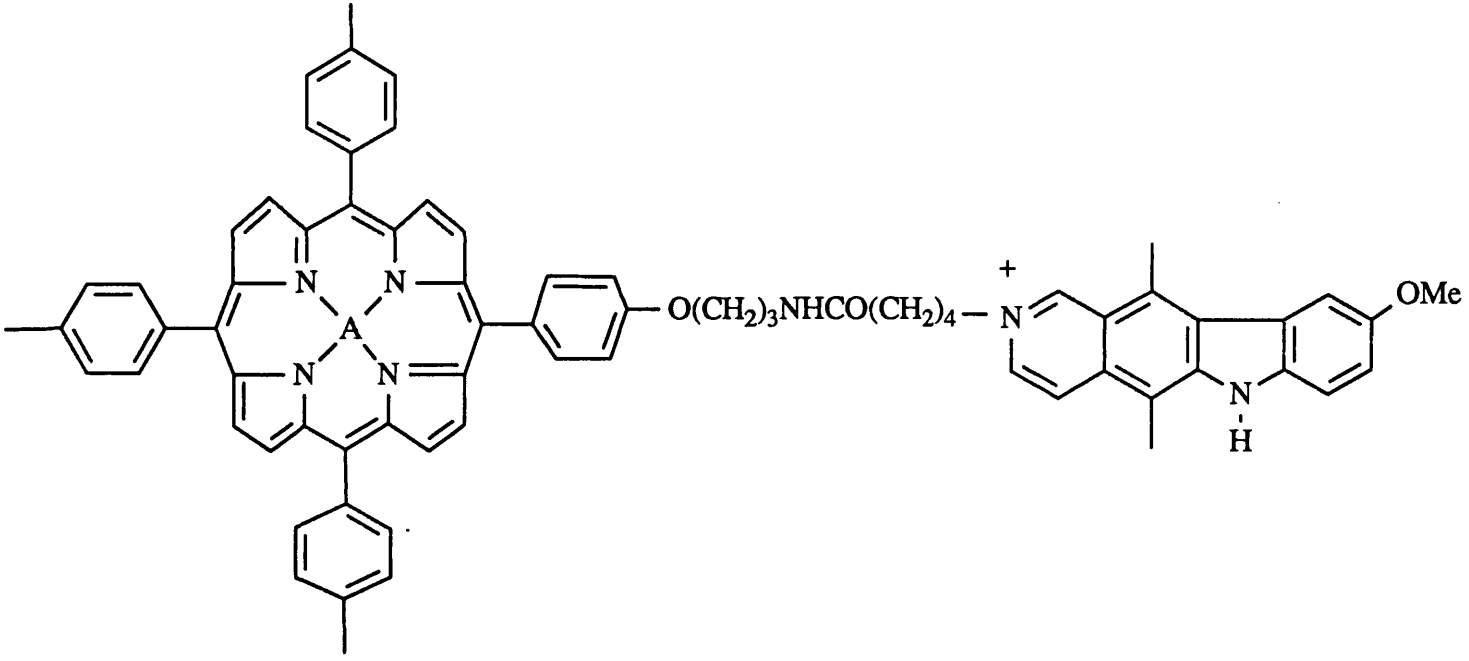
Scheme 36

Reacting the mixed anhydride (133) with the aminoporphyrin (134), using triethylamine as an acid trap, afforded the free base hydrid molecule (135). Metallation of the hybrid (135) is achieved by heating it with a large excess of the required metal salt in the presence of 2,4,6-collidine at 140°C. (Scheme 37).

Although the "metalloporphyrin-ellipticine" molecules (136a-c) exhibit efficient binding to DNA, no DNA breaks were experimentally observed. This could be a consequence of their low water solubility.



(134)



(135) $A = H_2$

(136) a A = Fe(III) - OAc ; b A = Mn(III) - OAc ; c A = Zn(II)

Scheme 37

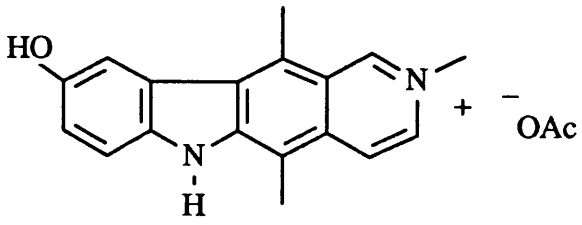
The Biochemical Properties of Ellipticine and its Derivatives

The antineoplastic activity of the ellipticines is now well documented,[4,78-84] but, although much information regarding the physical effects of ellipticine and its derivatives on the structure of DNA is known, the mechanism of their cytotoxicity action *in vivo* and *in vitro* is still not well understood.

A common feature of this class of compounds is their intercalative binding to DNA. Nevertheless, in various series of closely related derivatives, many compounds having the same apparent affintiy for DNA differ in their biological properties.[58,78]

The ability of ellipticine to intercalate into DNA was inititally established from viscosity, sedimentation and electric dichroism experiments[85], and later confirmed by ^1H n.m.r studies of a DNA-ellipticine complex[86]. In addition, Jain *et al.*[87] co-crystallised ellipticine with 5-iodocytidylyl(3'-5')guanosine.

All ellipticine derivatives are highly cytotoxic to malignant cultured cells[4]. Most of the 9-hydroxy derivatives are also active on standard experimental tumours[24]. The quaternised drug 2N-methyl-9-hydroxyellipticinium acetate (13) exhibits promising results for the treatment of osteolytic breast cancer metastases, kidney sarcoma, and hepatoma.[88,89]



(13)

The main reasons for interest in ellipticines for clinical purposes are their limited toxic side effects and their complete lack of hematological toxicity[90].

Although it is still not certain exactly what the role(s) of the ellipticine drugs are, three possible biological properties have been identified: (i) intercalation and binding to DNA and involvement with the normal functions of the topoisomerase enzymes which regulate DNA; (ii) oxidation to potential alkylating agents and (iii) the intracellular formation of radicals.

(i) **Intercalation and binding of DNA and Involvement with Topoisomerase**

The assumption that DNA may act as the primary target for ellipticines was initially based on the following physiochemical and biological evidence[91]: The size and shape of the ellipticine chromophore closely resemble those of a purine-pyrimidine complementary base pair, providing favourable conditions for its intercalation in double stranded DNA. Furthermore, the polycyclic aromatic character of the molecule may result in tight interactions with appropriately conformed hydrophobic regions in DNA.

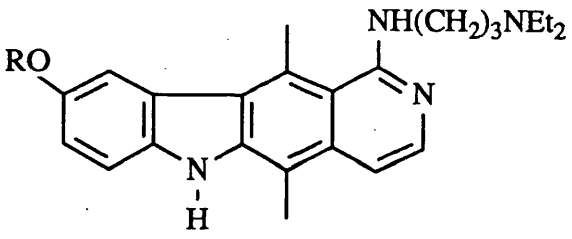
An indirect action on nucleic acids in cells also appeared to be likely because ellipticines have been found to interfere with the activity of the enzymes DNA polymerase, RNA polymerase,[91,92] RNA methylase[93] and, more recently, topoisomerase II[94]. These effects could be attributable either to the binding of the drugs to double-helical nucleic acids or to their direct effect on the enzymes.

On the basis of crystallographic data, hydroxylation of the ellipticine nucleus at position C-9 was predicted to increase the apparent binding affinity of the new derivatives to DNA,[58,84] through the appearance of a hydrogen bond between the phenolic proton and the negatively charged phosphates.[96] This assumption has been experimentally verified for both basic and quaternised ellipticines. Compared to their unhydroxylated counterparts, the 9-hydroxy derivatives exhibit a higher cytotoxicity towards L1210

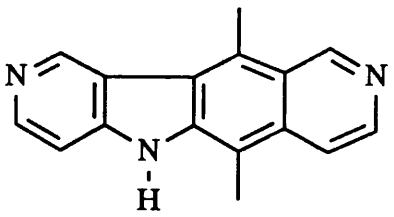
cultured cells.

However, many compounds in the series, including 9-aminoellipticine and 6N-alkylellipticinium derivatives, which have similar or even higher affintiy values for DNA, display low cytotoxic activity and no antitumour effect.

A number of ellipticines substitutes at C-1 by aminoalkylamino groups have been synthesised and their cytotoxicity assessed.[97] The best compound in the series is the 9-methoxylated derivative [(137), R = Me]. The hydroxy analogue [(137), R = H] is less useful and it is possible that the methoxy compound is acting at a different biological target.



(137)



(138)

This also appears to be the case for the azaellipticine (138)[98], which is a candidate for clinical evaluation.

One important fact is that whereas all ellipticines which show activity *in vivo* exhibit DNA binding, DNA binding alone, as noted for 9-aminoellipticine[25], does not guarantee anticancer activity. Hence, additional parameters appear to be required for the expression of the cytotoxicity of ellipticines.

The hypothesis that intercalation of ellipticines between DNA base pairs could be responsible for antitumour activity has been supported by the fact that all ellipticine derivatives not able to intercalate exhibit a low cytotoxicity against cultured cells and no

significant antitumour activity. Non-intercalative ellipticines have been provided by structural modifications either by the hydrogenation of the pyridine ring which distorts the planar ellipticine nucleus or the substitution of the hydrogen at position C-9 by bulkier functional groups such as a bromine atom or a nitro function.

The major ambiguity in the interpretation of such results is that the inability of drugs to intercalate is always accompanied by the loss of other properties such as the ability to generate oxyradicals and to undergo covalent binding to macromolecules. These effects will be discussed later.

Hence, the work undertaken so far clearly indicates that intercalation appears to be a necessary, but not a complete requirement for antitumour activity.[99]

Ross *et al.*[100] observed a unique type of DNA strand break, termed a protein associated strand break, following exposure of ellipticine to mouse leukaemia L1210 cells. Single strand DNA breaks also occurred, but only prior to DNA enzymatic deproteinisation. These protein associated strand breaks were further shown to have the protein tightly, if not covalently, bound to the DNA in a spatial and stoichiometric relationship. This suggests that the protein is bound at or near the break site.

It has also been demonstrated[101] that these protein associated DNA breaks are not observed for non-intercalating DNA binding compounds.

Other results obtained by various groups of workers indicate that several of the more successful drugs in clinical use are compounds that cause potential breaks in the nuclear DNA of cells.[93,94,102,103] A considerable amount of evidence indicates that the drug induced DNA breaks occur through alteration of topoisomerase II activity.

DNA topoisomerases are enzymes which are important in the regulation of DNA topology and facilitate such processes as DNA replication, transcription, transposition and

viral integration.[104,105] Two types of topoisomerases are known, type I and type II. The biological role of type I topoisomerase seems to centre around single strand fission and reunification, but its mechanism of action is poorly understood and as yet, there is little known about it which could be used to aid the improvement of the design of anticancer drugs.

More data is available regarding type II topoisomerase. This enzyme possesses the ability to transiently break and reseal both DNA strands simultaneously. Also, by virtue of a phosphotyrosine linkage, it can bind to free DNA ends during the breakage-reunion process.

It is thought that ellipticines, and other drugs, prevent the enzyme from resealing the breaks it has introduced in the DNA, which result in the formation of a cleavable DNA-topoisomerase complex.[106-109]

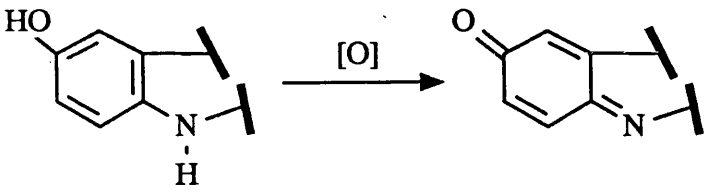
Liu *et al.*[110] have shown that the enzyme remains bound at one end of the cleavage site *via* a phosphotyrosine bond. DNA cleavage by topoisomerase, however, does not require a topologically restrained substrate, thus suggesting that drug intercalation may not be an essential requirement. This has now been confirmed[110] by the demonstration that some non-intercalative drugs also induce protein linked DNA breaks, both i*n vivo* and *in vitro*.

As an alternative,it has been suggested[110] that drug intercalation into DNA enables the drugs to interact specifically with topoisomerase II, and thus interfere with the resealing action of topoisomerase II by stabilisation of the cleavable complex.

It is noteworthy that, so far, the ability to induce cleavable complexes is only observed with ellipticines bearing an hydroxyl group at C-9.

The ellipticine molecule, thus substituted, has two oxidisable groups in a *para*

relationship, and is therefore a substrate for peroxidases which are known to convert it into an iminoquinone. (Scheme 39). The oxidation of 9-hydroxyellipiticines to their corresponding iminoquinones has been demonstrated to occur *in vitro*[111] and this has led to the suggestion of another possible mechanism for cytotoxicity.



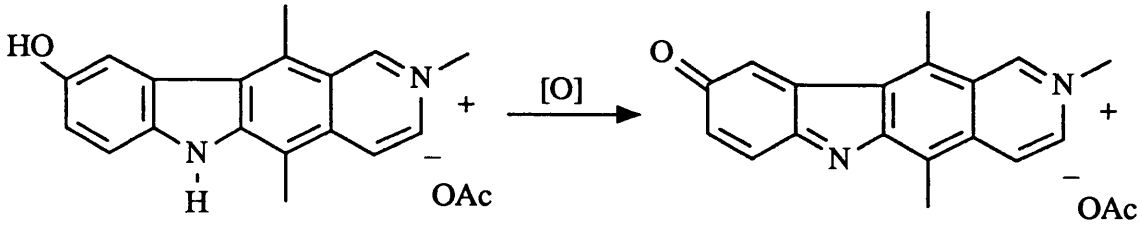
Scheme 39

(ii) **Oxidation to Potential Alkylating Agents**

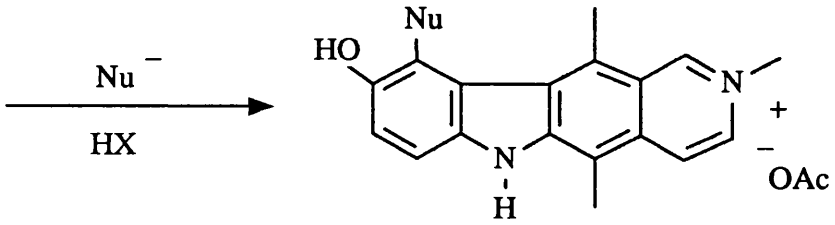
Auclair *et al.*[111] have shown that if 9-hydroxy-2-methylellipticinium acetate (13) is treated either with horse radish peroxidase or with human myeloperoxidase, in the presence of hydrogen peroxide, a phenoxy radical is generated which decays by a dismutation process to yield the iminoquinone (139). This species acts to trap potential nucleophiles such as pyridine, cysteine and glutathione regiospecifically at the sterically more hindered but electronically favoured[112] C-10 position[113]. (Scheme 40).

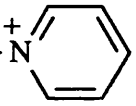
Meunier *et al.*[112] have recently reported electrochemical data which make it clear that all hydroxylated ellipticine derivatives are easily oxidised. This correlates with the facile peroxidase oxidation of these molecules by the horse radish peroxidase/H_2O_2 system.

It was also reported that when the phenolic group (i.e. the 9-hydroxy of ellipticine) is blocked or absent, then the oxidation potential is higher and may not then be achieved biochemically or at least the rate of oxidation is reduced.



(13) (139)



(140) Nu = 

(141) Nu = $-SCH_2(CO_2H)NHR$

(142) Nu = $-SCH_2CH(CONHCH_2CO_2H)NHCO(CH_2)_2CH(CO_2H)NH_2$

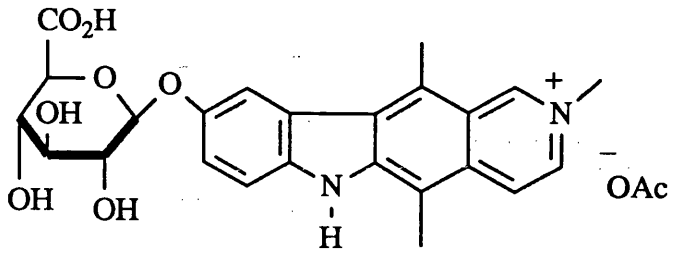
Scheme 40

The adducts (140), (141) and (142) have been isolated and tested, *in vitro*, on leukaemia L1210 cells and found to be less cytotoxic than the starting compound (13)[114]

Meunier[114] argued that the biological activity of the adducts were in line with the possibility that the iminoquinones represented the activated forms of the 9-hydroxyellipticines, and that the molecules were subsequently alkylated by biological nucleophiles. This species (139) behaves as an electrophile, analogous to models proposed for other anticancer drugs.[115]

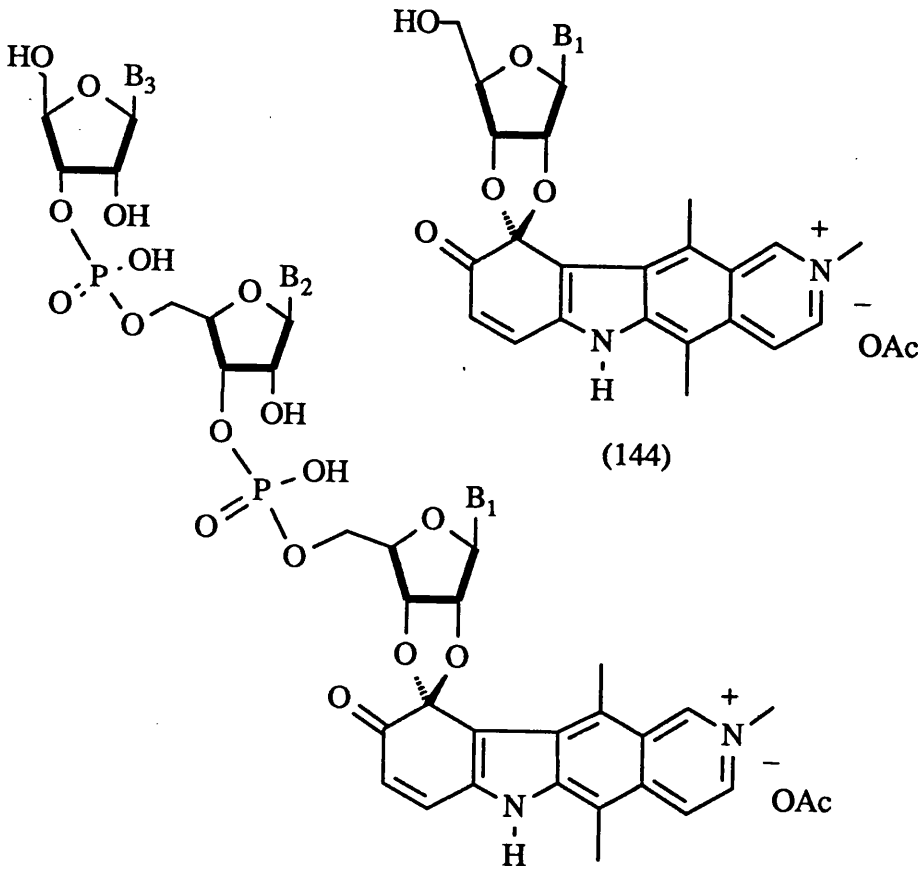
Interestingly, the urinary metabolites of the drug (13) in mammals are the cysteinyl adduct ((141), R=H), its N-acetylcysteinyl derivative ((141), R = Ac), the O-glucuronide (143) and the S-glutathione (142). The formation of both C- and O-bonded compounds

indicates that two competing metabolic pathways are operating in parallel.



(143)

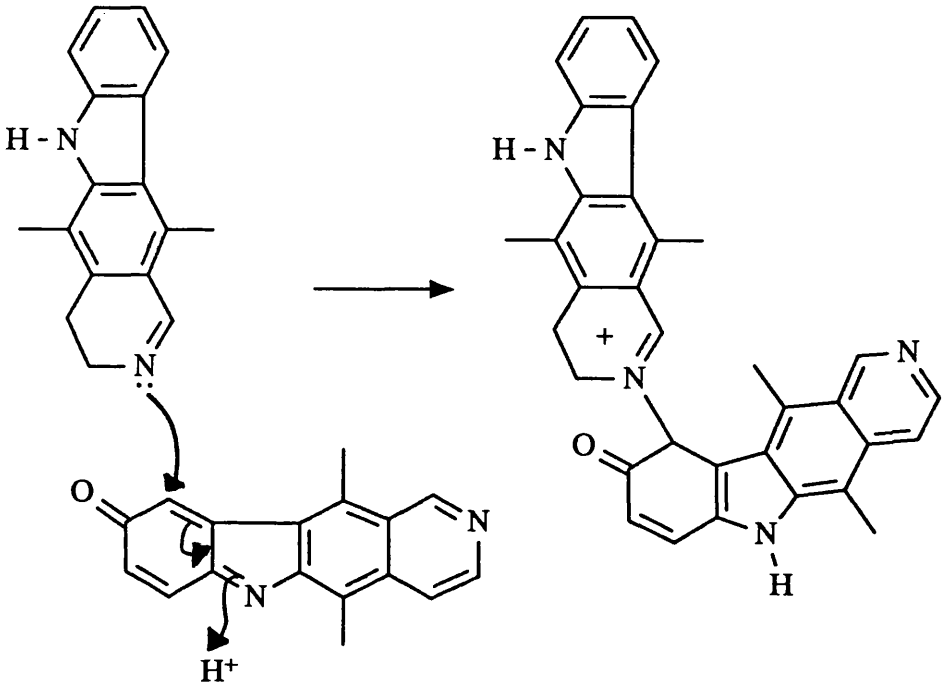
Further studies[116-120] have established that, under oxidative conditions, the quaternised iminoquinone (139) reacts with ribonucleosides and ribonucleotides to produce adducts of the type (144) and (145) respectively, where B_1, B_2 and B_3 represent various bases found in nucleic acids.



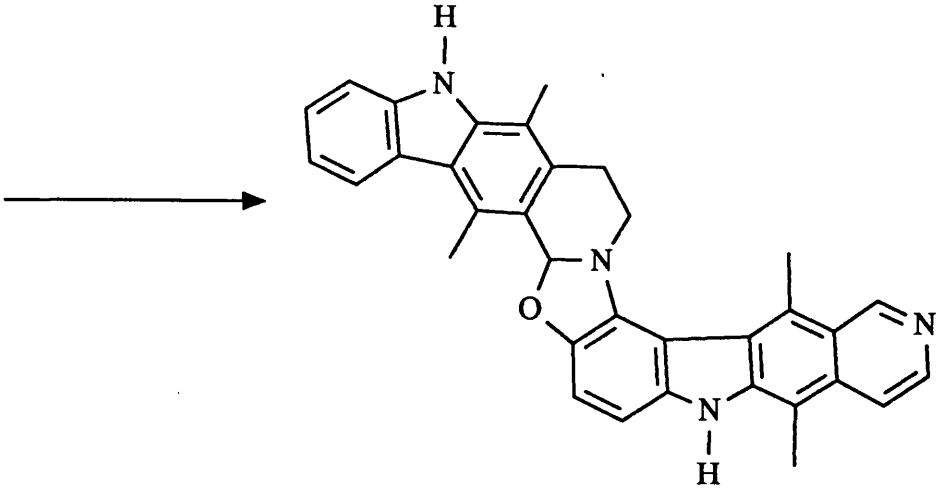
(144)

(145)

(148)



(147)



(146)

Scheme 41

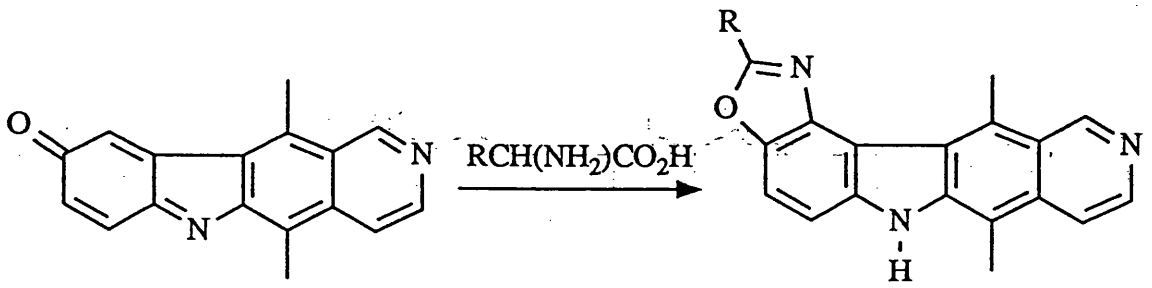
Koch *et al.*[121] have recently reported the occurrence of the first ellipticine-derived bisindole, strellidimine (146), isolated from *Strychnos dinklagei* (Loganiaceae).

The isolation of strellidimine is interesting from both biological and chemical points of view since the reaction sequence involved in its formation seems similar to that implied in the alkylation of nucleosides by ellipticine derivatives.

From a biogenic point of view, strellidimine (146) may be considered as arising from a condensation of the two monomeric units which co-occur in *S. dinklagei* bark. The mechanism shown in Scheme 41 can be envisaged for the dimerisation : oxidation of 9-hydroxyellipticine leads to the electrophilic iminoquinone (147) which undergoes addition of dihydroellipticine (148) through its nucleophilic dihydropyridine nitrogen. The quaternary adduct obtained rearranges, leading to the fused oxazole system of (146).

In view of these results it has been suggested that the hydroxylated ellipticines may exert some of their antitumour activity through alkylation of either t- or m- RNA, leading to an inhibition of protein synthesis.

It has been shown[122] recently, however, that adducts of the type (149) are formed between the iminoquinone (147) [from 9-hydroxyellipticine] and alkylamines (RCH_2NH_2) under oxidative conditions, or amino acids [$RCH(NH_2)CO_2H$]. (Scheme 42).



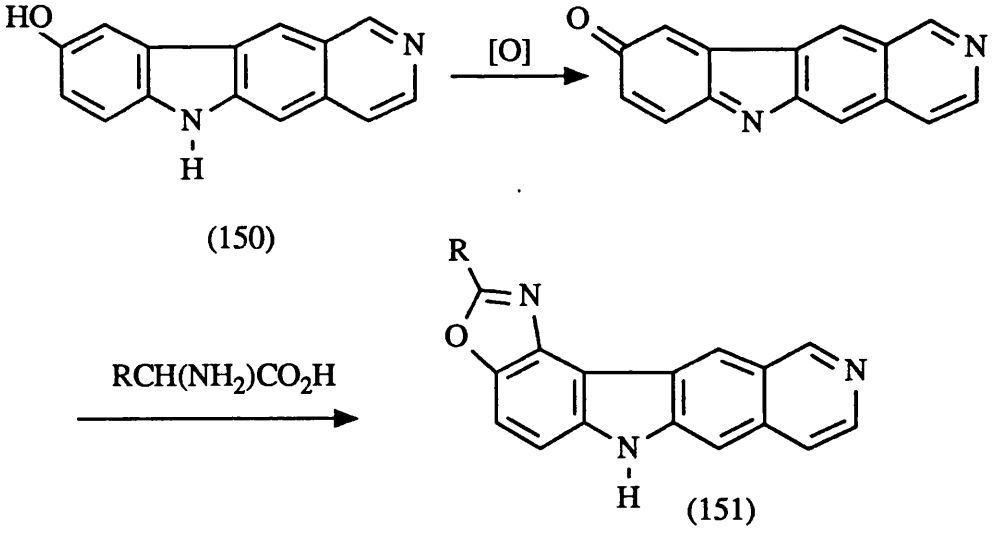
(147) (149)

Scheme 42

It is therefore possible that the oxidised forms of the 9-hydroxyellipticines might act to trap biogenic amines, amino acids, peptides and proteins, *in vivo*, and thus inhibit protein biosynthesis.[123] Similarly, *in vitro* experiments have demonstrated that bovine serum albumin (BSA) and other proteins bind to 9-hydroxy-N-2-methylellipticinium acetate (13) irresversibly under bio-oxidative conditions.[123]

Conflicting evidence has been reported by Roy *et al.*[124], stating that if (13) is incubated with L1210 murine leukaemia cells, covalent binding occurs to both DNA and RNA but not to proteins.

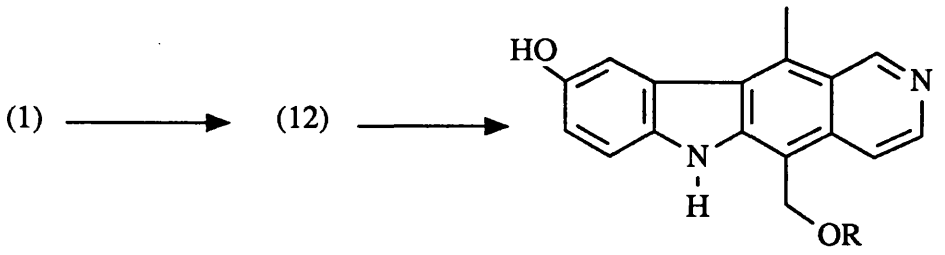
However, despite the above findings, the validity of the various hypotheses has recently been challenged by Archer *et al.*[25] He has shown that 9-hydroxy-6H-pyrido[4,3-*b*]carbazole (150) is inactive against murine P388 lymphocytic leukaemia. The absence of the methyl groups does not, however, prevent oxidation to an iminoquinone which will then react with an amino acid to give a Potier type adduct (151). (Scheme 43).



Scheme 43

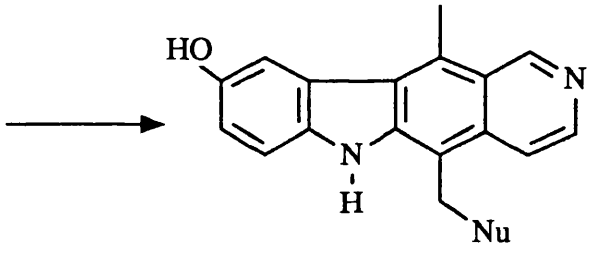
For anticancer action, Archer argues that a 5-methyl group is necessary. He suggests that ellipticine (1) is metabolically converted to 9-hydroxyellipticine (12), a

known metabolite of (1).[22,125] This species, in turn, is enzymically converted first to the carbinol (152), which is then transformed into a phosphate or sulphate (153). This compound, which now possesses a good leaving group, alkylates a nucleophilic macromolecule such as DNA or possibly topoisomerase II to give the adduct (154). (Scheme 44).



(152) R = H

(153) R = PO_3H^- or SO_3^-

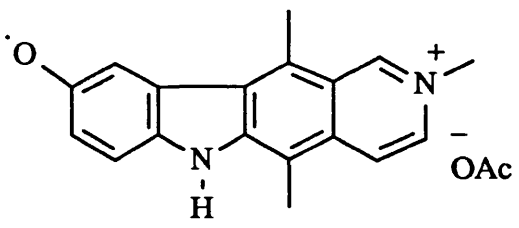


(154)

Scheme 44

(iii) **The Intracellular Formation of Radicals**

As described earlier, 9-hydroxyellipticines can be oxidised to generate phenoxy radicals (155) which can decay by a dismutation process to yield iminoquinones (139).

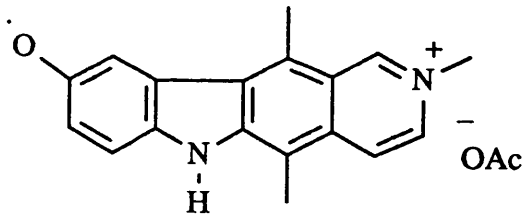


(155)

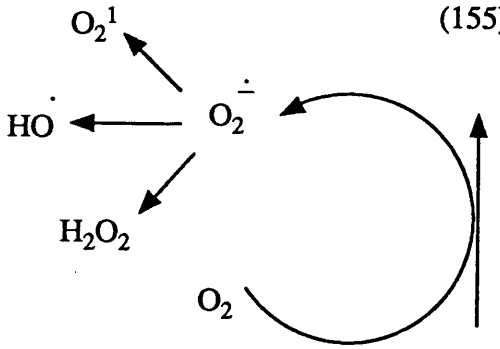
Such phenoxy radicals could be responsible for DNA strand breaks, resulting in irreversible damage to the DNA.[126] The cytotoxic activity of a number of benzanthraquinones and N-heterocyclic quinones has also been explained on the basis of the formation of transitory phenoxy radicals.[127,128]

The formation of the phenoxy radicals, in the case of 9-hydroxyellipticine and (13) has been shown by *in vitro* experiments in the presence of NaOH/DMSO or peroxidase $-H_2O_2$[111]. However, phenoxy radicals are also reported to be very stable[129] and therefore not responsible for DNA strand breaks.[8]

The *in vivo* formation of these phenoxy radicals could be explained by the reduction of molecular oxygen to superoxide ions. Such species could be responsible for DNA strand breaks. For example, the reaction of superoxide ions with water could furnish highly reactive hydroxyl radicals (·OH) which could damage DNA and may also initiate lipid peroxidation and subsequently result in the cell damage.[130] (Scheme 45).



(155)



(13)

Scheme 45

In conclusion,there is evidence that the cytotoxicity of antitumour agents operates at the DNA level and that DNA serves as the ultimate target for these compounds.

Furthermore, it has become clear that most classes of antitumour drugs, including ellipticines, display multiple properties causing DNA damage.

At the moment, there is no evidence that the ellipticines currently available show selectivity of action. This could change, however, as biological targets are recognised and become more clearly defined, and particularly as our understanding of the role of the topoisomerases in regulating the behaviour of nucleic acids develops.

Discussion and Results

A detailed series of computer molecular modelling determinations were recently carried out[131,132] on the docking modes of ellipticines within DNA. The results demonstrated that only substitution at the 4-,5-, and 7-positions does not result in steric clashes within the base pair pockets. A free NH group at position 6 is required for anticancer effect as it has already been shown[2] that N-6 alkylated ellipticines are less active than the parent compound.

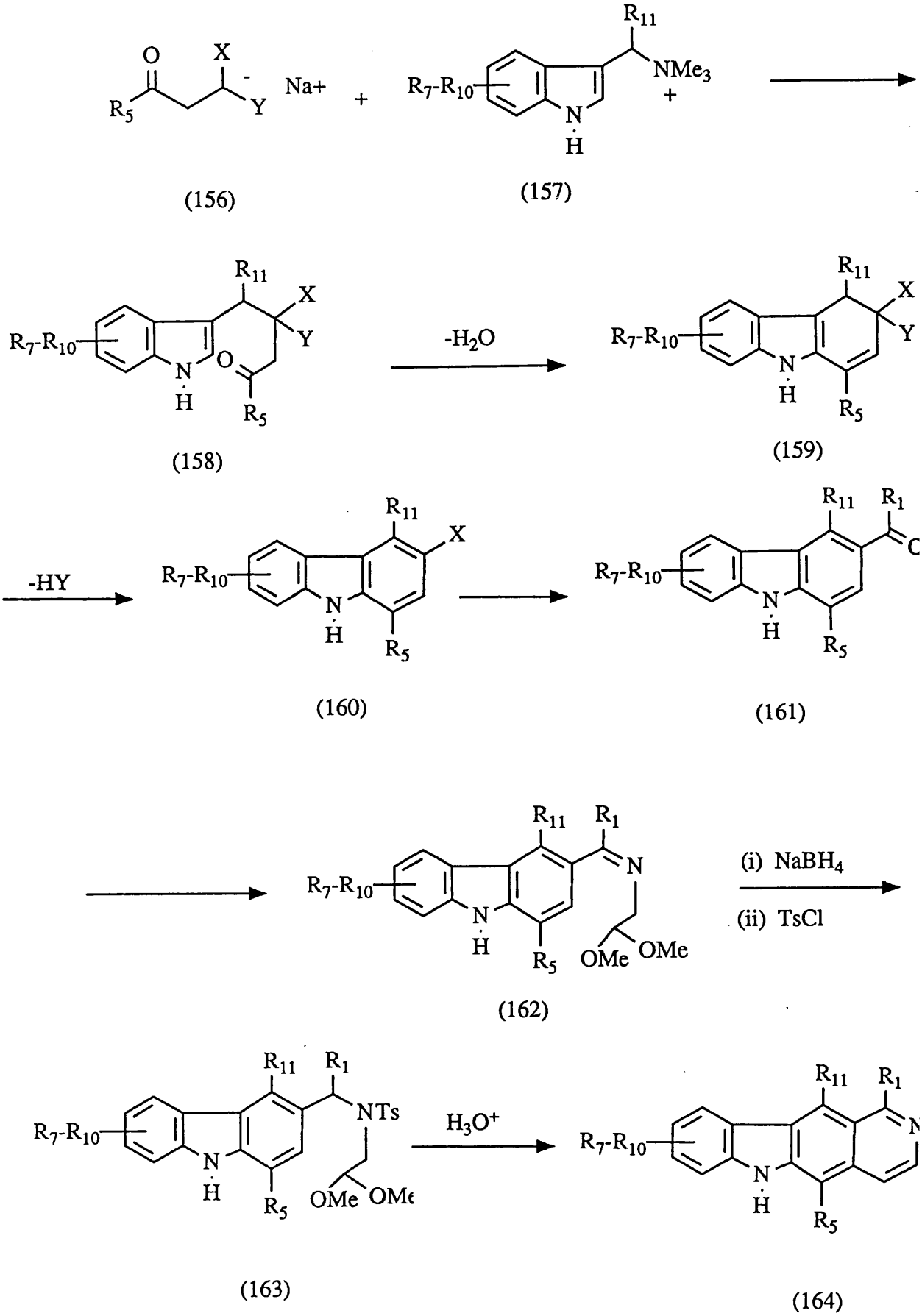
An approach to pyrido[4,3-*b*]carbazoles which is both short and specifically designed to provide access to 4-,5- and 7-substituted analogues, was recently initiated by a worker in our group at Bath[134].

The proposed route is outlined in Scheme 46.

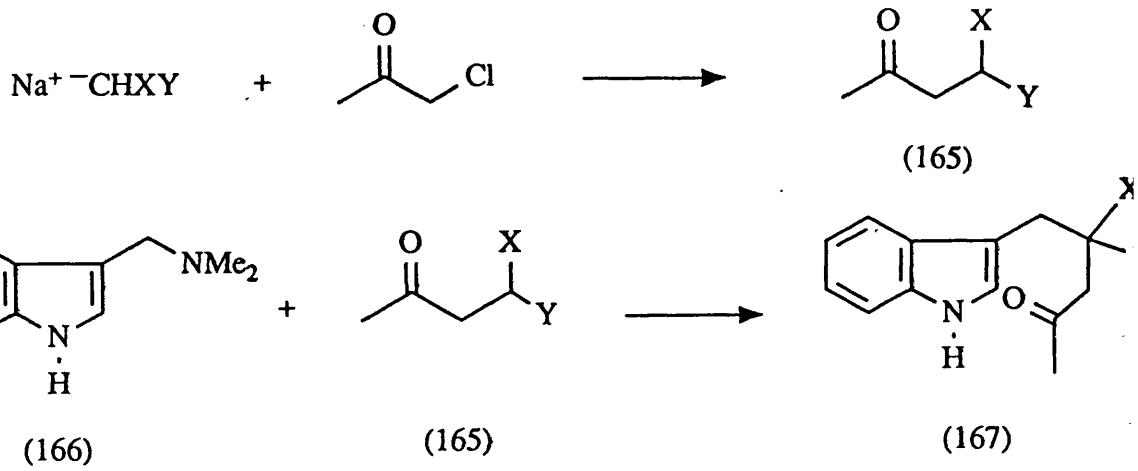
The route outlined involves the synthesis of a specifically substituted acyl carbazole (161), which can then be elaborated, by a modified[62,63] 'D-ring' synthesis[64] to the required 6H-pyrido[4,3-*b*]carbazole (164).

The first step in the synthetic route involves the synthesis of the suitably substituted ketone (156). The criteria for the choice of X and Y are as follows: They must both be electron withdrawing groups to exclusively form the anion required for reaction with the gramine quaternary salt (157); Y must be a group that can be eliminated to effect the aromatisation of dihydrocarbazole (159) to the carbazole (160); X must either be an acyl group or a unit that can easily be converted into an acyl group.

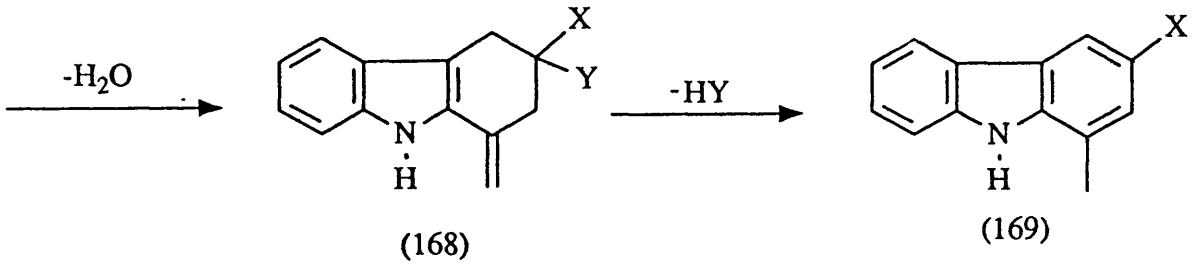
To test the feasibility of this methodology, a model study was undertaken to synthesise the natural product olivacine (2) (Scheme 47).

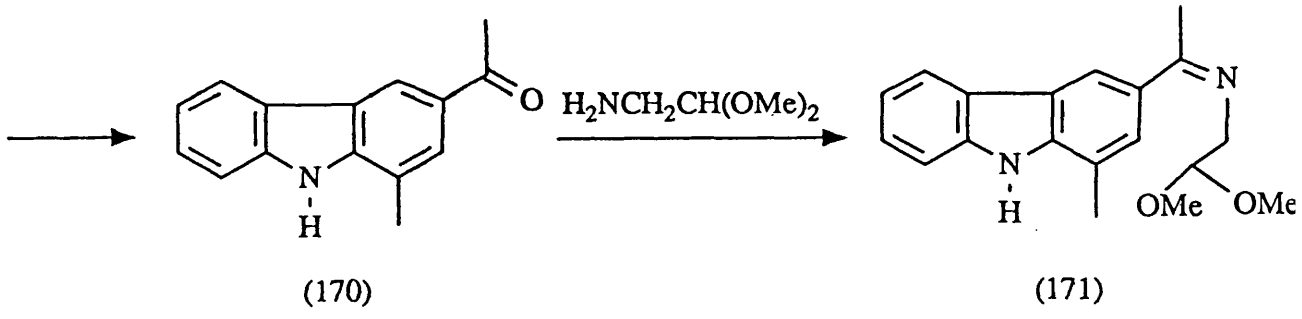


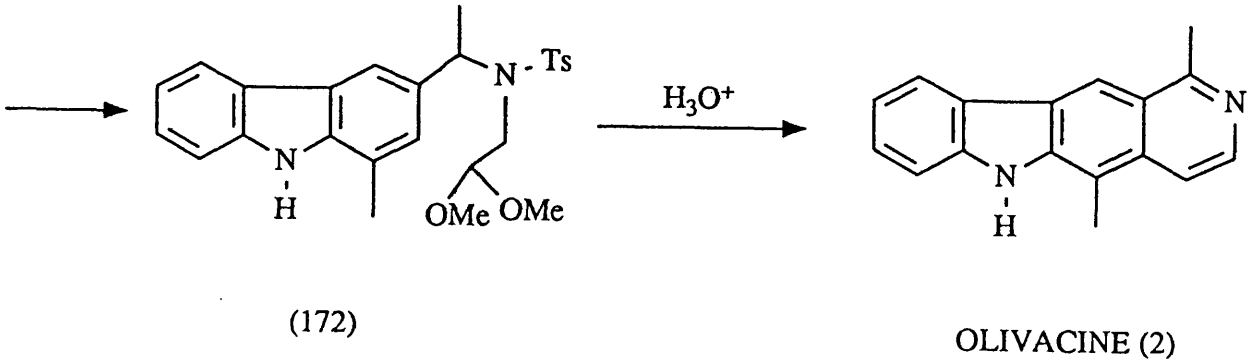
Scheme 46



(a) X=CN,Y=CN (b) X=CN,Y=CO_2Et (c) X=$COCH_3$,Y=CO_2Et



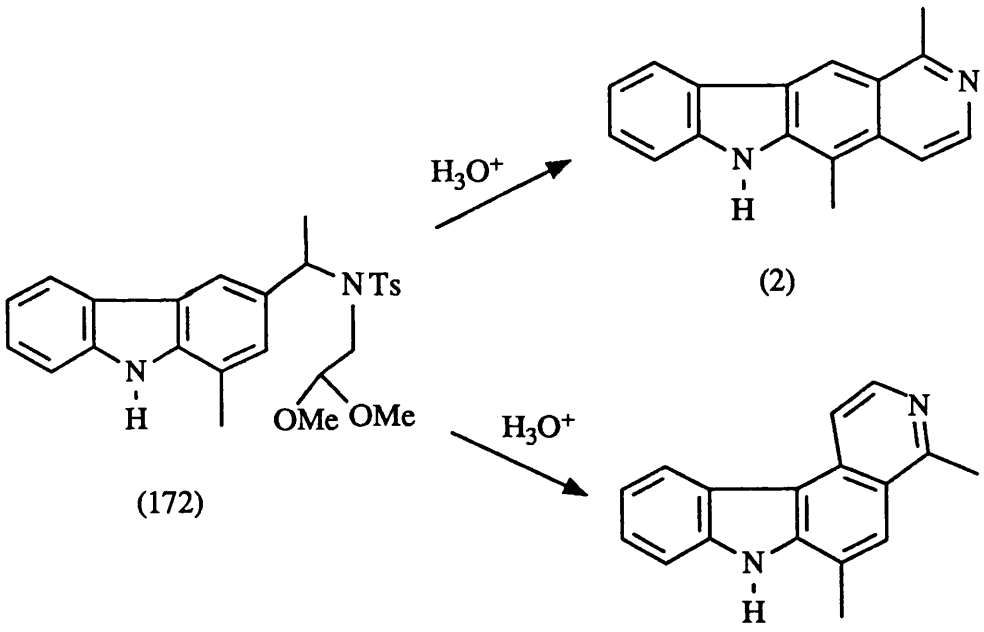




Scheme 47

Olivacine (2) was chosen as the target because the required starting material,gramine (166), is cheap and readily available. Also, the intermediate 3-acetyl-1-methylcarbazole (170) has recently been synthesised and converted to olivacine (2) in low yield[65].

Interestingly, the penultimate compound to olivacine (2) in Scheme 47, is the acetal (172). This compound has two possible sites for cyclisation, to give olivacine (2) or its angular isomer (100) (Scheme 48).



Scheme 48

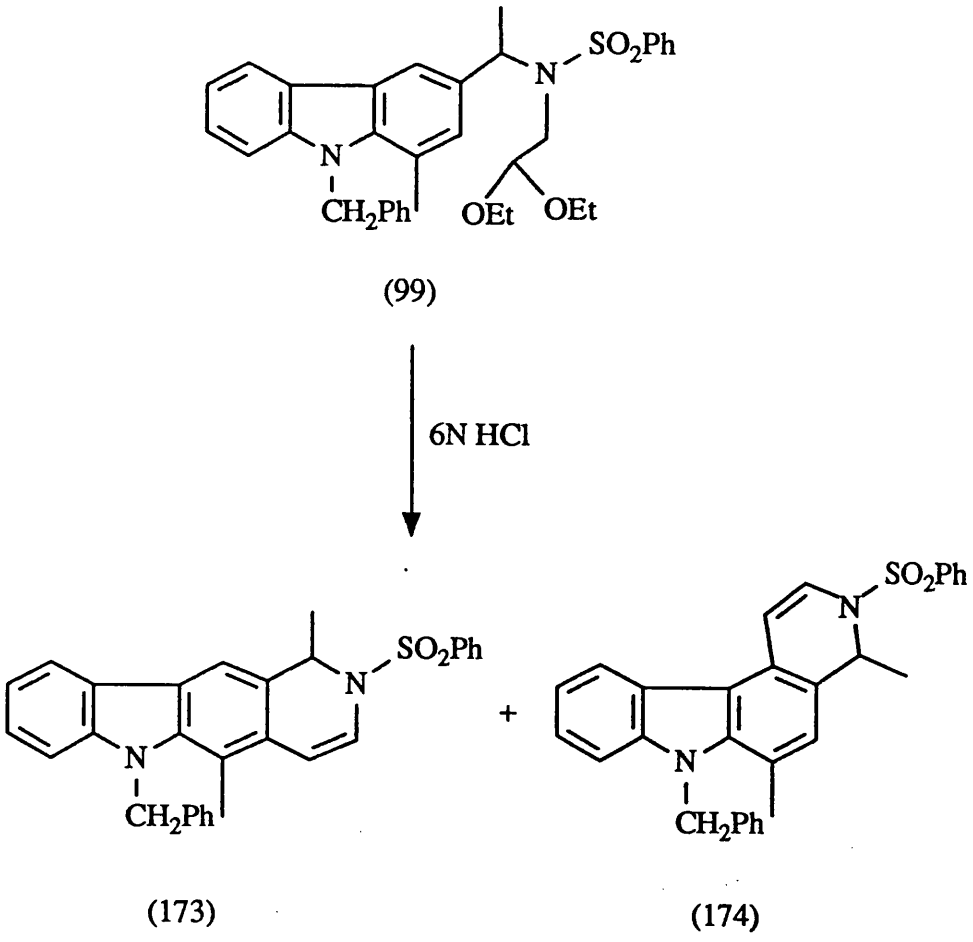
However, the angular product (100) was not reported by Narasimham and Gokhale[65]. It was stated that the tosyl compound (172) was converted to olivacine (2) in 65% yield.

This is surprising as there is contradictory precedent in the literature. Okuyama

and co-workers[66] attempted to synthesise olivacine (2) from the precursor (99).

The reagents and conditions employed were as follows:
(i) 6N HCl/dioxane; (ii) Na/liquid NH_3 and (iii) Pd-C/Tetraline. Both products (2) and (100) were obtained in yields of 12% and 10% respectively.

The requirement for a three step procedure rather than simple acid treatment followed, by deprotection implies that the first, acid mediated, reaction causes the formation of the benzyl-dihydropyridocarbazoles (173) and (174) (Scheme 49).



(99)

(173)

(174)

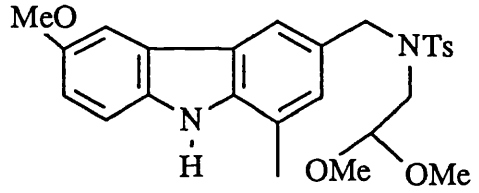
Scheme 49

The second step, treatment of this product with Na/liquid NH_3, would then be

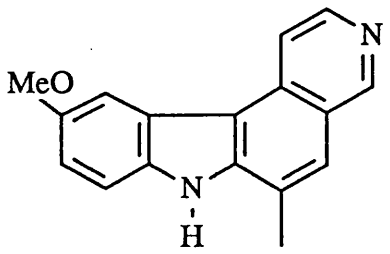
needed to remove the N-phenylsulfonyl group.

NH-Dihydroisoquinolines are known to aromatise spontaneously by disproportionation, giving *both* the isoquinoline and the tetrahydroisoquinoline.This limits the yield of each product to 50% so it is therefore better to react the mixed products with a dehydrogenating agent such as palladium on charcoal in tetralin, thereby producing only the isoquinoline.

Another interesting discrepancy between the work of Narasimham and Gokhale,and other workers, is the report by Viel and co-workers[137] that the cyclisation of the amine (175) gives a 20% yield of the pyrido[3,4,-*c*]carbazole (176).



(175)



(176)

The first step in our synthesis of the 3-acetylcarbazole (170) was the formation of suitably substituted ketones (165).

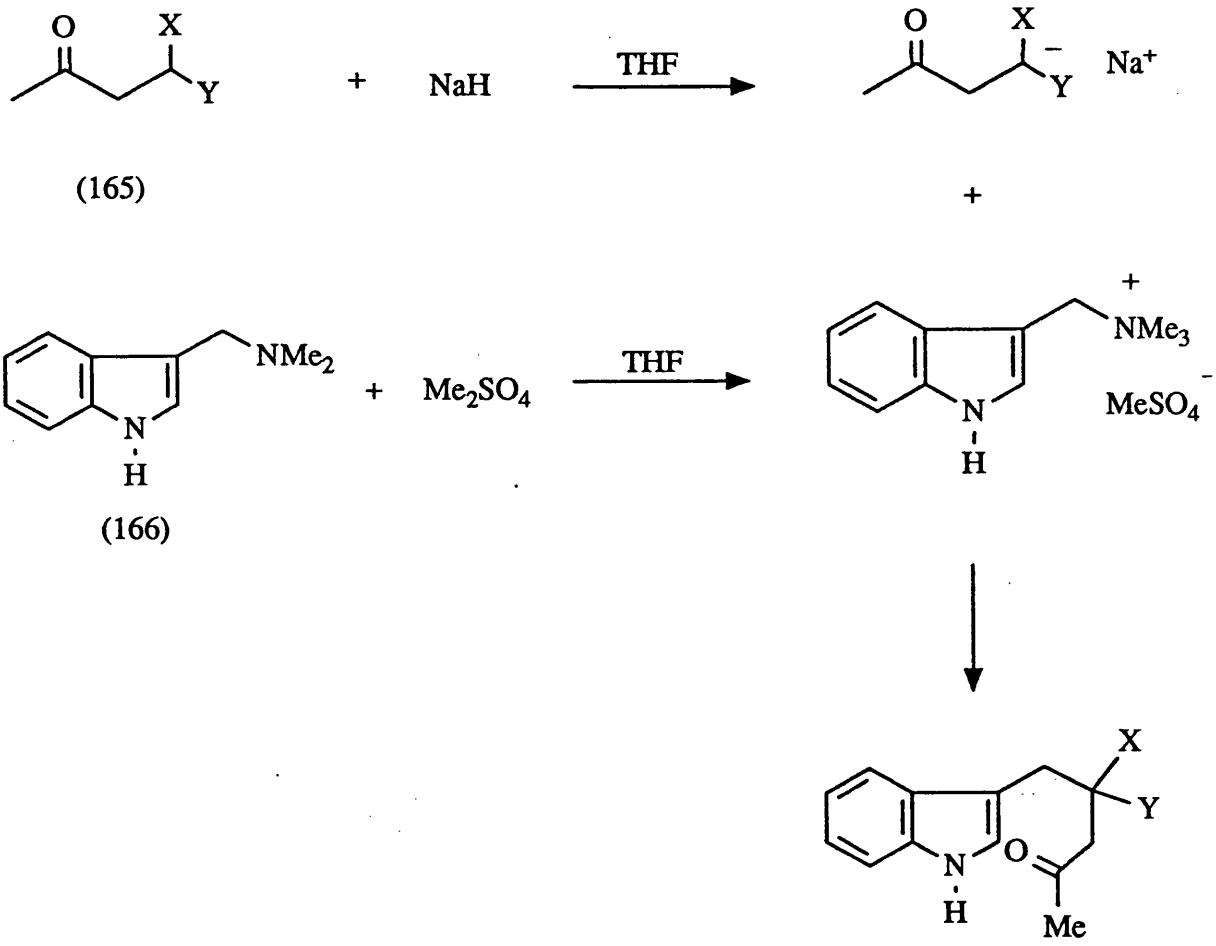
Bearing in mind the criteria outlined earlier, three ketones were deemed useful substrates: 2-cyano-4-oxopentanonitrile (165a); ethyl 2-cyano-4-oxopentanoate (165b) and ethyl 2-acetyl-4-oxopentanoate (165c).

The synthesis of these compounds follow from the general reaction of chloroacetone with the respective anions of malononitrile (X = Y = CN); ethyl cyanoacetate (X = CN, Y = CO_2Et) and ethyl acetoacetate (X = CO_2Et, Y = $COCH_3$) (Scheme 47).

Ketones (165a) and (165b) had previously been synthesised in these laboratories[134]. The procedures were repeated to give the products in 79% and 64% yield respectively on multigram scale.

The ketone (165c) was previously reported in the literature[135]. This procedure was repeated to give (165c) in 66% yield, again on multigram scale.

With these ketones in hand, an efficient method of condensing them with gramine (166) was considered. The previous worker[134], Dr. Hogan, had achieved this type of reaction by forming the anion of the ketone and reacting it with the quaternary salt of gramine in dry THF.(Scheme 50).



(166)

(167a) X=Y=CN

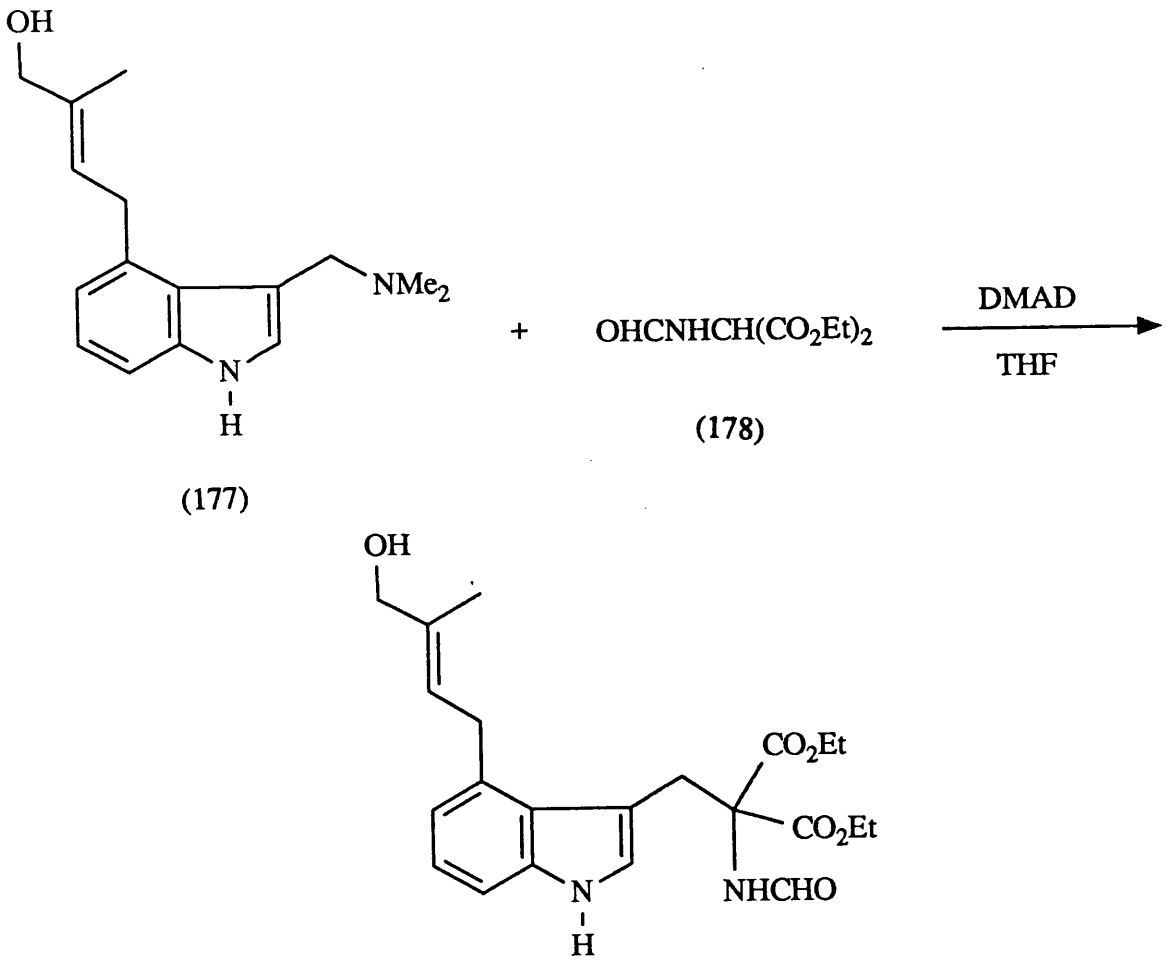
(167b) X=CN,Y=CO_2Et

Scheme 50

This method worked well in our hands and yields of 84% for (167a) (using HMPA as co-solvent) and 99% for (167b) were achieved.

The quaternary salt of gramine (166) is an insoluble gum and this created practical problems with stirring, especially during large scale reactions.

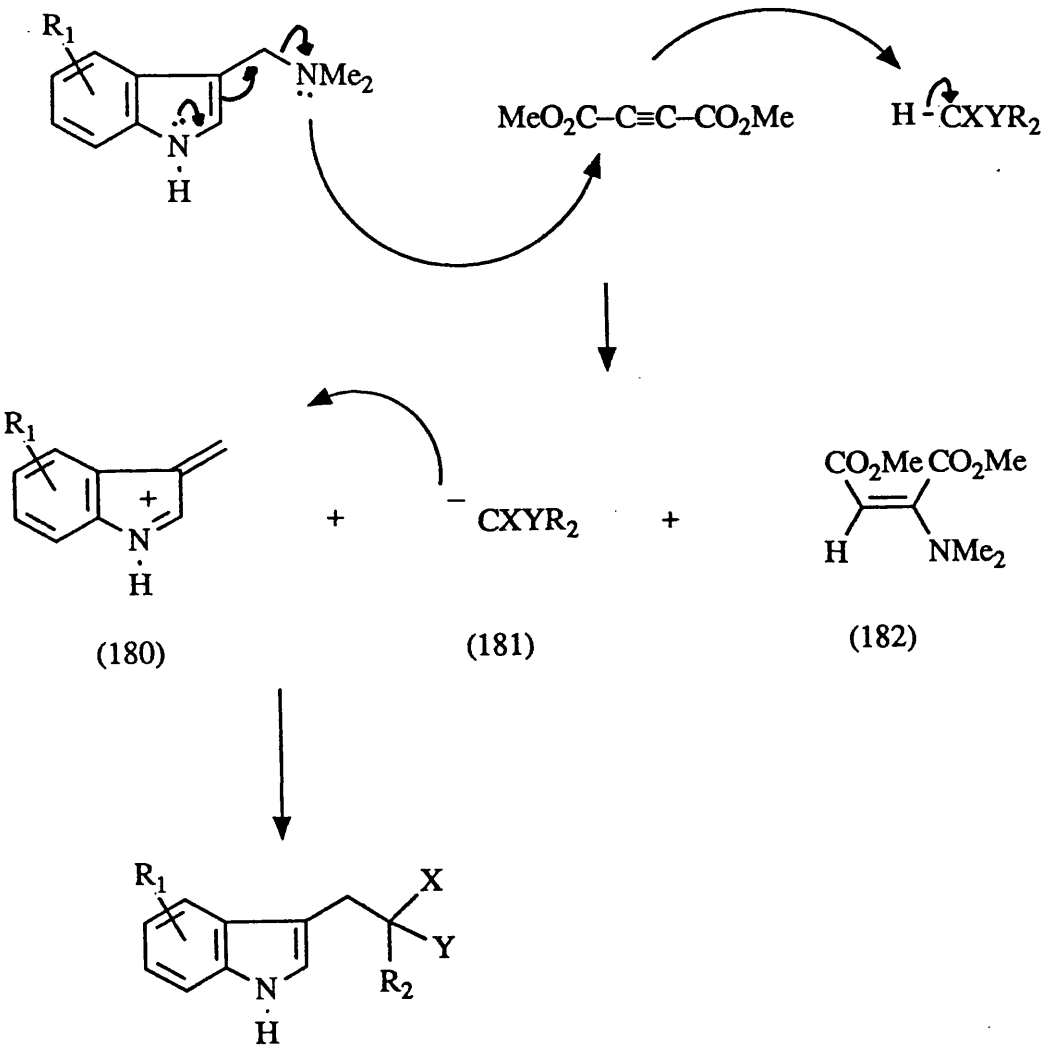
Another method that we tried was modelled on a literature method: Plieninger *et al.*[136] achieved a similar reaction, between a gramine (177) and a malonate type compound (178), utilising dimethyl acetylenedicarboxylate (DMAD) as reagent (Scheme 51).



Scheme 51

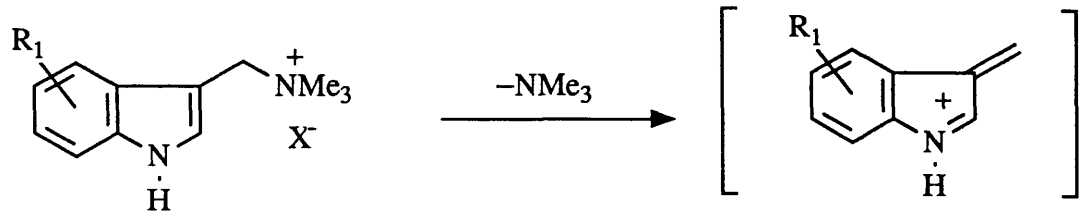
The reaction in THF at ambient temperature, gave the prodct (179) in 72% yield.

One equivalent of DMAD is used and the mechanism of the reaction is considered to involve the following steps. (Scheme 52).

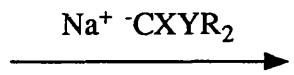


Scheme 52

This mechanism gives similar intermediates (180) and (181) as that most frequently proposed[138] for the reaction involving gramine quaternary salts. (Scheme 53).



(180)



(183)

Scheme 53

Plieninger purified the product (179) (Scheme 51) by column chromatography after evaporating the reaction solvent. No mention was given to the isolation or the detection of the expected by-product (182).

This method seemed a simpler and cleaner alternative to that which uses the quaternary salts of gramine (166) and we applied it to the synthesis of compounds (167a), (167b) and (167c).

The reactions were performed by adding a solution of the ketone (165) and DMAD (1 equivalent each) in THF to a cooled solution of gramine (166) (1.1 equivalent) in THF.

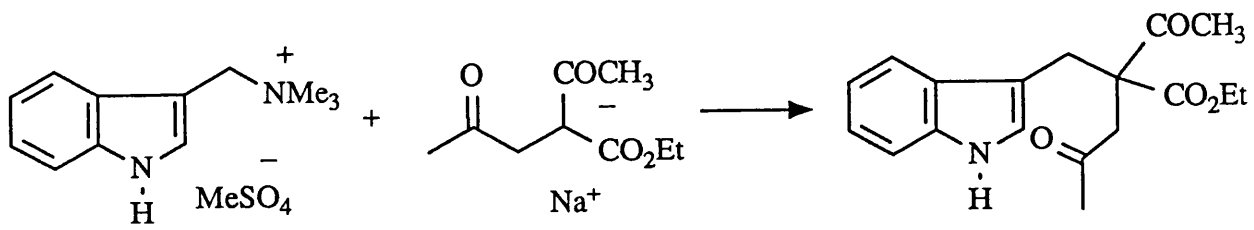
The reactions were monitored by t.l.c. and in each case, consumption of the ketone (165) was complete after 1-2h. The indole compounds (167a) and (167b) were isolated in 71% and 98% yield respectively, on a multigram scale.

However, when the procedure was used for the synthesis of the indole (167c), the product was contaminated with another compound. Through extensive column

chromatography, it was possible to partially separate the two compounds, which proved to be the required product (167c) and the enamine (182) (Scheme 52).

The enamine is actually an enaminoester and acidic work-up did not remove it from the indole (167c). Consequently, this procedure was deemed unsatisfactory for the preparation of (167c).

Fortunately, the pure indole (167c) was available in 79% yield by the reaction of the anion of (165c) with the methosulphate salt of gramine (166) (Scheme 54).



(167c)

Scheme 54

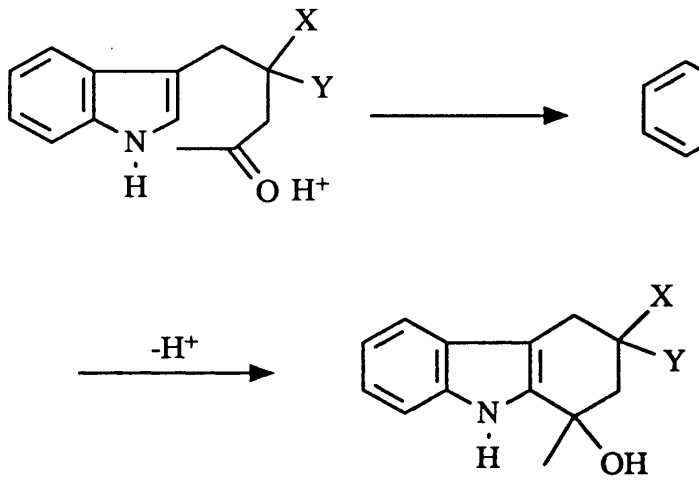
The next step in the synthetic sequence was the acid catalysed cyclisation of the indoles (167) to the dihydrocarbazoles (168).

The conditions of choice for these transformations involved heating them in refluxing 50% aqueous acetic acid.[134]

There are two possible mechanisms for this ring closure. The simplest involves direct attack onto the protonated ketone at the 2-position of indole, followed by loss of a proton (Scheme 55).

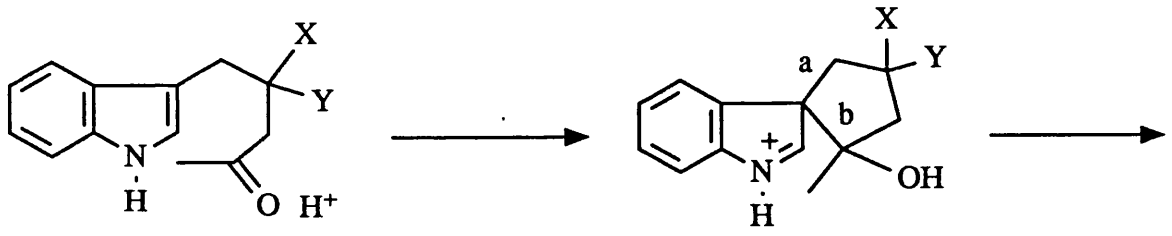
The second course, often argued by Jackson and co-workers,[139,140] suggests that the initial substitution occurs at the more reactive 3-position of the indole ring to give

a 3,3'-spirocyclic indolenine (185). This is then followed by a Wagner-Meerwein[141] type [1,2] shift to afford the cation (186) which deprotonates to the tricycle (184) (Scheme 56).

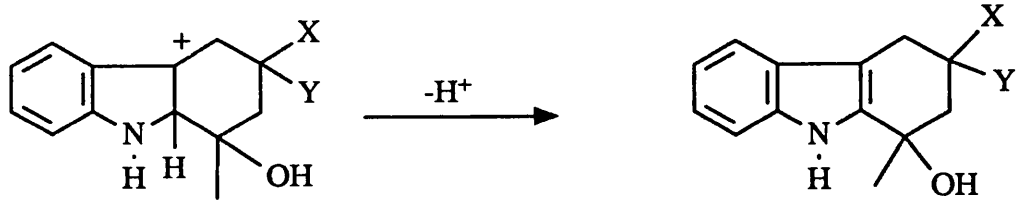


(184)

Scheme 55



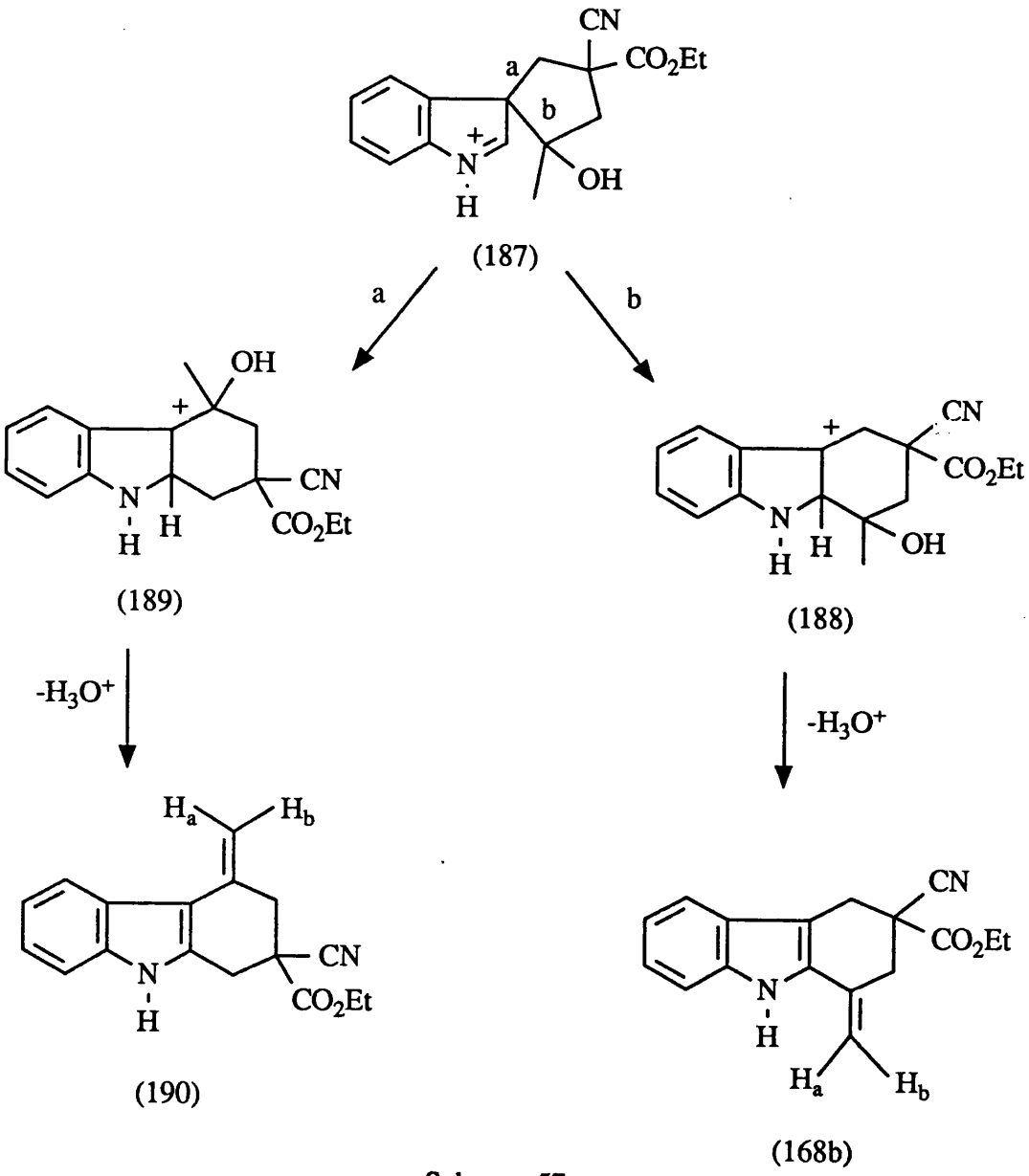
(185)



(186) (184)

Scheme 56

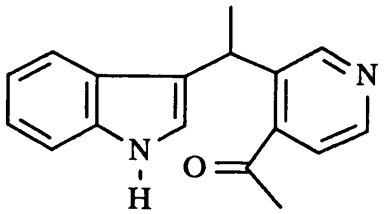
In substituted precursors such as ours, a problem could arise if the wrong bond migrates *i.e.* bond (a) instead of bond (b) (Scheme 57). The resultant carbazole would have the substituents on the 1,4- and 2,3- positions inverted.



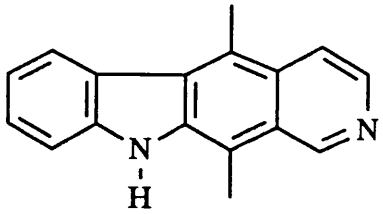
Scheme 57

Migration of the correct bond (b) should be facilitated by electron release from the oxygen according to precedents cited by Jackson and Smith[139].

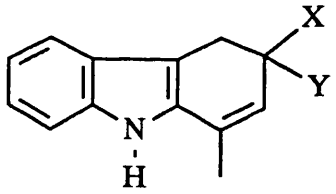
Sainsbury *et al.*[142] have also studied this problem with the ring closure of ketone (191). They have shown, on the basis of spectral evidence, that ellipticine and not isoellipticine (51) is obtained as the sole product.



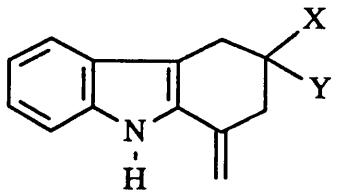
(191)



(51)



(192)

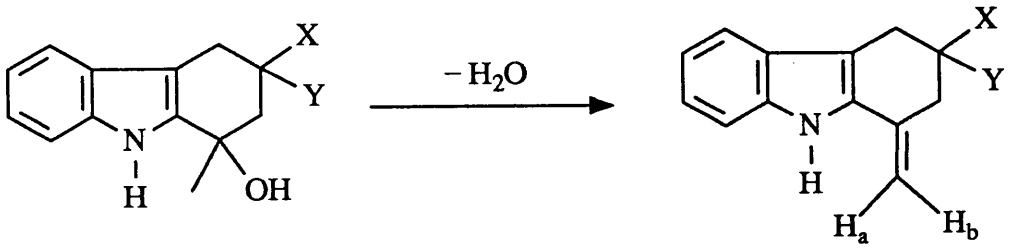


(168)

Heating the indoles (167a) and (167b) in 50% aqueous acetic acid produced the carbazoles (168a) and (168b) in 99% and 98% yield respectively.

Although the expected product was the endocyclic 3,4-dihydrocarbazole (192), ^{1}H n.m.r. analysis indicated retention of both the chain methylene groups of the precursors (167) and two, not one, olefinic protons. The only explanation for these data is that dehydration of the cyclised alcohol (184) had occurred through loss of a terminal proton producing an exocyclic double bond, and leading to the isomeric

structure (168). (Scheme 58).



(184) (168)

Scheme 58

A comparison of models of the two isomers did not suggest any steric reasons why the exocyclic double bond should predominate.

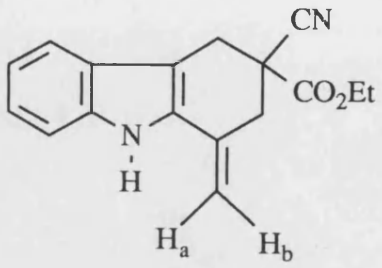
To check the authenticity of structure (168b), a nuclear Overhauser enhancement (n.O.e.) difference ^1H n.m.r. spectrum was taken. The compound was irradiated at the indole nitrogen proton frequency (8.32 ppm). Should the compound have structure (168b), then the signal of one of the two olefinic protons (Ha) should, because of its spacial proximity, be enhanced. With compound (190) (Scheme 57), this would not be the case. The result of this n.m.r. experiment confirmed 3-cyano-3-ethoxycarbonyl-1,2,3,4-tetrahydro-1-methylenecar bazole (168b) to be the sole product, as an enhancement of 8% was observed at 5.30 ppm, the resonance frequency of the olefinic proton , H_a, (Spectrum 1).

When the indole compound (167c) was subjected to boiling in 50% aqueous acetic acid, a mixture of two compounds homogeneous by t.l.c, was obtained.

Inspection of the ^1H n.m.r. spectrum of the mixture revealed two singlets at 5.04 ppm (1H) and 5.24 (1H) ppm together with a doublet at 5.88 ppm (1H). The rest of the spectrum was also indicative of a 1:1 mixture of the isomeric compunds (168c) and (193).

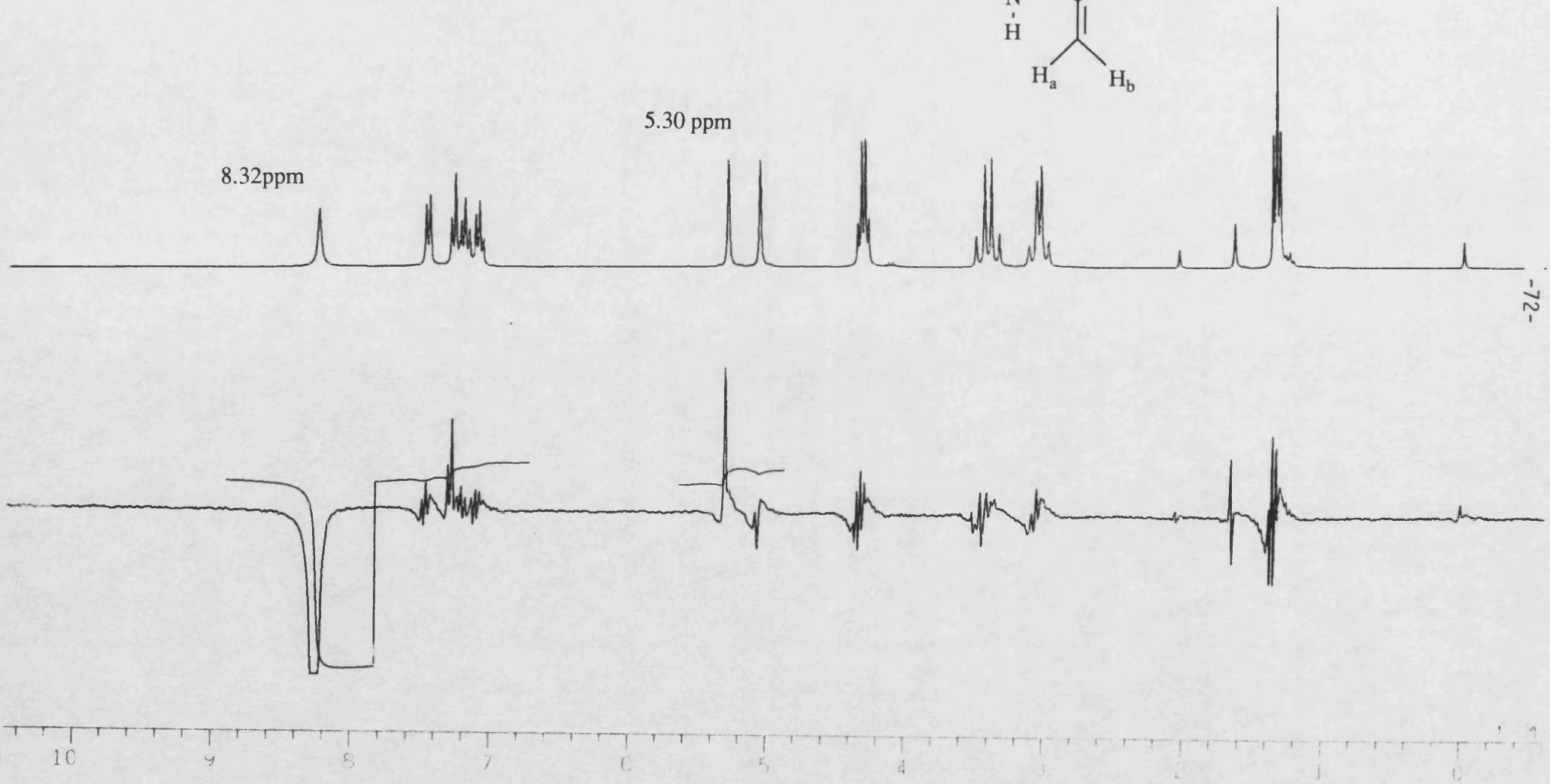
Spectrum One

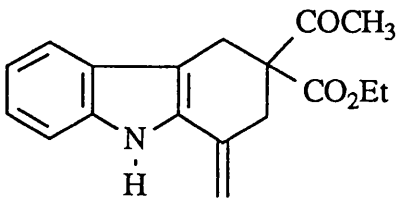
n.O.e. experiment on (168b)



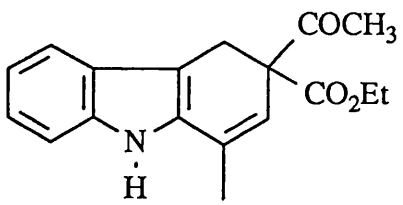
5.30 ppm

8.32ppm





(168c)



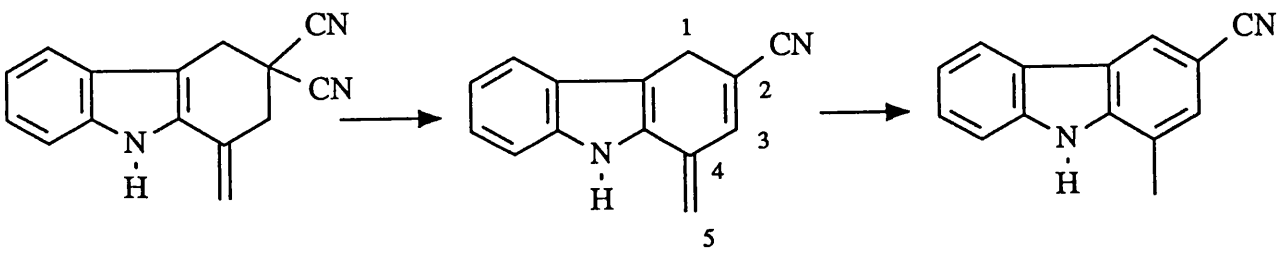
(193)

The mixture was isolated as an oil from which pure (193) could be obtained as a colourless solid by crystallisation from ethyl acetate/pet.ether. However, the mixture could be used in subsequent experiments without further purification.

The required carbazoles (169) could now be obtained by elimination of one of the groups X or Y from the compounds (168).

The dinitrile (168a) was converted smoothly to the required carbazole (169a) by simple thermolysis.[134]

A typical experiment was is follows:
3,3-dicyano-1,2,3,4-tetrahydro-1-methylenecarbazole (168a) was absorbed onto silica and heated to 250°C under a stream of nitrogen for one hour. On extraction and chromatography, 3-cyano-1-methylcarbazole (169a) was obtained in 22-61% yield. The reaction, whether ionic or radical in nature, presumably proceeds *via* the elimination of hydrogen cyanide and a subsequent 1,5-hydrogen shift to afford the more stable, fully aromatised carbazole (169a). (Scheme 59).



(168a) (169a)

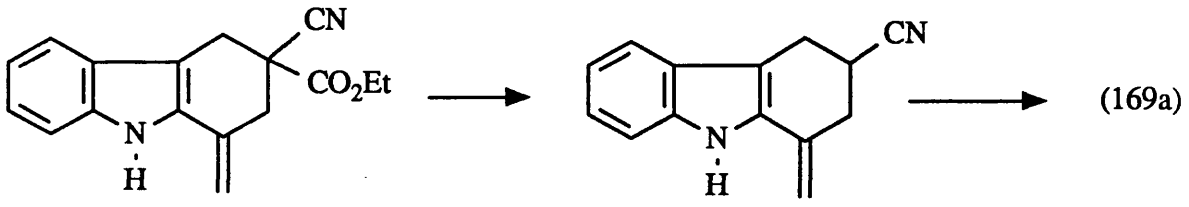
Scheme 59

A similar thermolysis was performed on 3-cyano-3-ethoxycarbonyl-1,2,3,4-tetrahydro-1-methylenecarbazole (168b). After two hours heating and subsequent extraction and chromatography of the product, two compounds were isolated. The expected product, 3-ethoxycarbonyl-1-methylcarbazole (169b) was obtained in 30-55% yield along with 10% of the cyanocarbazole (169a).

The formation of the latter compound can be explained by the occurrence of water in the acidic silica gel which hydrolyses the ester to the corresponding acid. This then decarboxylates under the high temperature of the reaction conditions.

It should be noted that the yields in these thermolysis reactions were quite variable and often dropped quite significantly when the reaction was carried out on greater than about ten gram scale.

An alternative method to obtain the cyanocarbazole (169a) would be to de-ethoxycarbonylate the ester (168b) and then to oxidise the product nitrile (194). (Scheme 60).



(168b) (194)

Scheme 60

Traditionally, this type of transformation has been effected *via* a base or acid mediated hydrolysis, followed by a thermal decarboxylation of the product acid or diacid. If another, non-activated, ester functionality is present in the molecule it is then necessary to re-esterify it, once the decarboxylation step has been achieved.

A process developed by Krapcho and his co-workers[143,144] involves the use of water, water with added salts (*eg* LiCl, NaCl, KCN), or anhydrous salts in dipolar aprotic media such as dimethyl sulfoxide. Under these conditions, activated esters such as malonate, β-keto and α-cyano esters are dealkoxycarbonylated (Scheme 61). The pathway outlined in Scheme 62 appears to be the dominant mechanistic route for the de-ethoxycarbonylation of disubstituted malonate esters in the presence of KCN and wet dipolar aprotic solvents.

When our substrate (168b) was heated at 160°C with lithium chloride (one equivalent) and water (one equivalent) in dimethyl sulfoxide for 48 hours, 3-cyano-1,2,3,4-tetrahydro-1-methylenecarbazole (194) was obtained in 50% yield. A small amount of the aromatic compound (169a) was also isolated from the reaction.

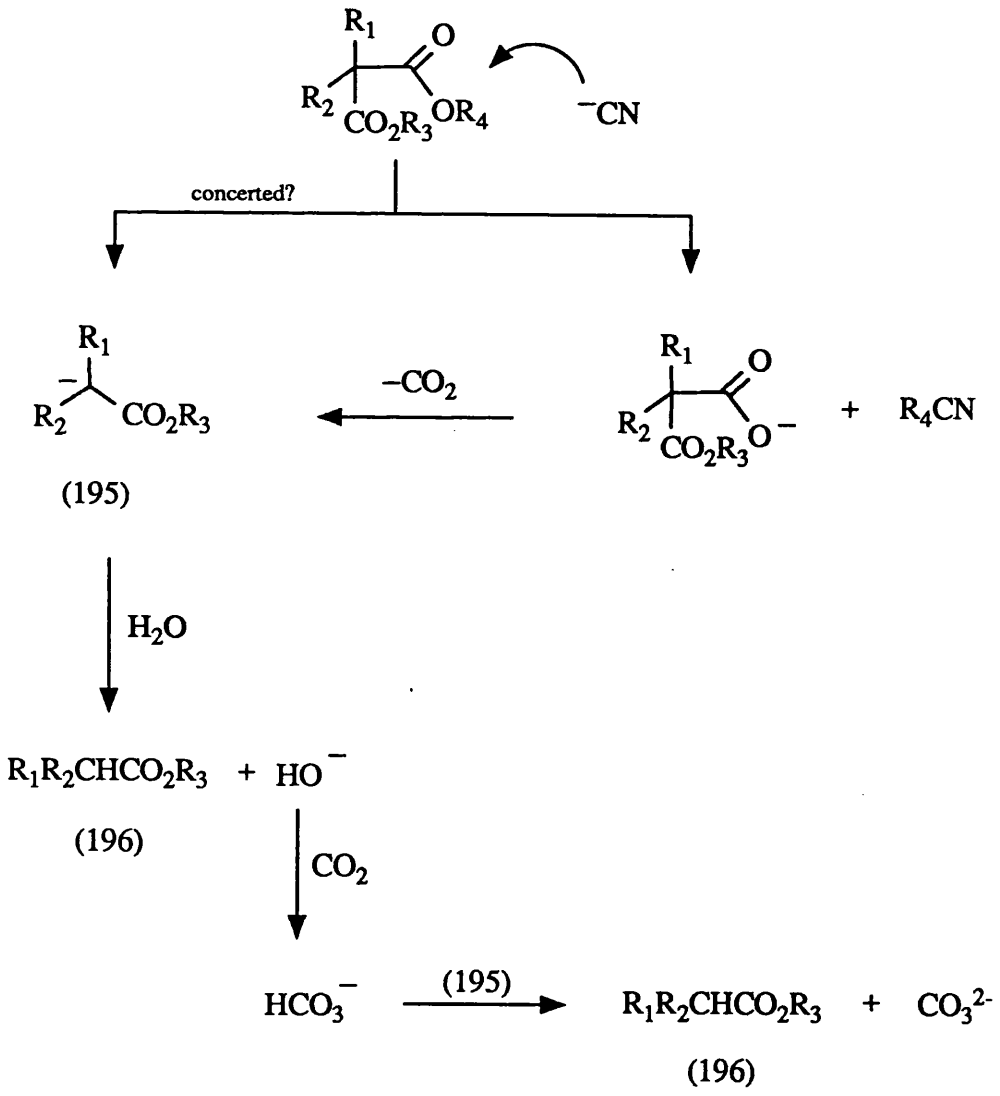
The formation of the fully aromatic compound (169a) must have been due to a thermal disproportionation of the intermediate (194), although we did not detect the corresponding tetrahydrocarbazole. The pure compound (194) was oxidised to the carbazole (169a) by boiling with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dry benzene. After 14 hours, the required carbazole (169a) was isolated in 80% yield.

To improve the yield in our reaction by avoiding losses due to disproportionation, the crude product from the de-ethoxycarbonylation reaction was oxidised with DDQ.

The required carbazole (169a) was now isolated in an overall yield of 75% for

X = -CO_2R , -COR , -CN , -SO_2R .

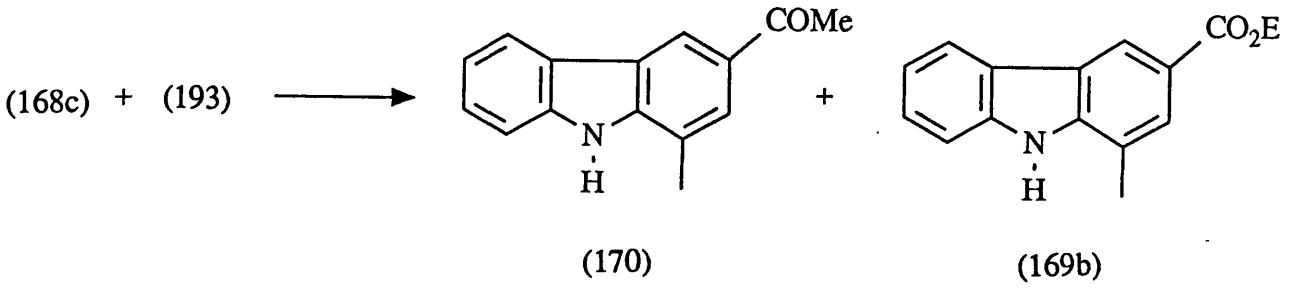
Scheme 61



Scheme 62

the two steps.

When the mixture of (168c) and (193) was heated at 120°C with lithium chloride, water and DMSO for 48 hours, the two compounds (169b) and (170) were isolated in 20% and 15% yield respectively. (Scheme 63).

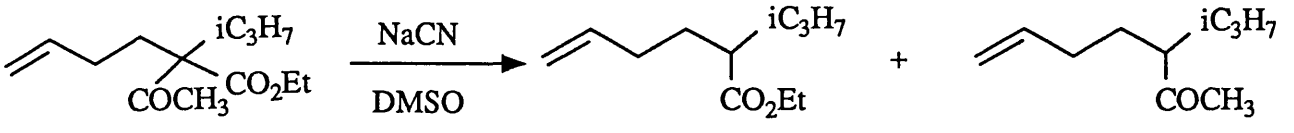


(170) (169b)

Scheme 63

The ketone (170) was formed by the expected de-ethoxycarbonylation, followed by thermal disproportionation.

However, the formation of the ester (169b) must have occurred by (a) a deacylation, and (b) a thermal disproportionation reaction. There is precedent for this result. Brocard *et al.*[145] obtained a similar outcome whilst attempting to de-ethoxycarbonylate the β-keto ester (197). (Scheme 64).



(197) 20% 70%

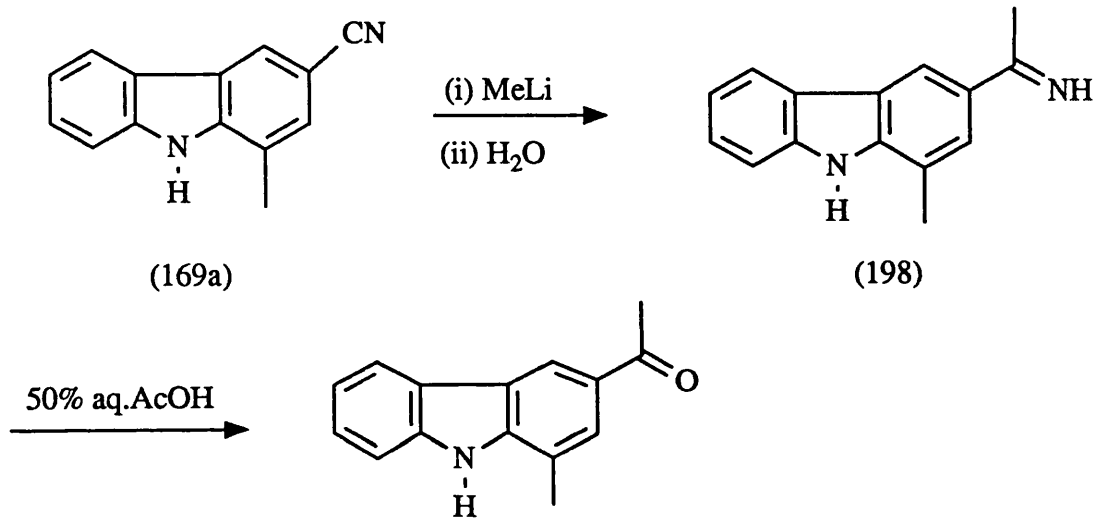
Scheme 64

The first target compound of this project, 3-acetyl-1-methylcarbazole (170), was thus

synthesised.

It was also prepared by the following methods:

Reaction of the nitrile (169a) with 2.2 equivalents of methyl lithium,[134] followed by acid hydrolysis of the intermediate imine (198) produced the ketone (170) in 98% yield. (Scheme 65).



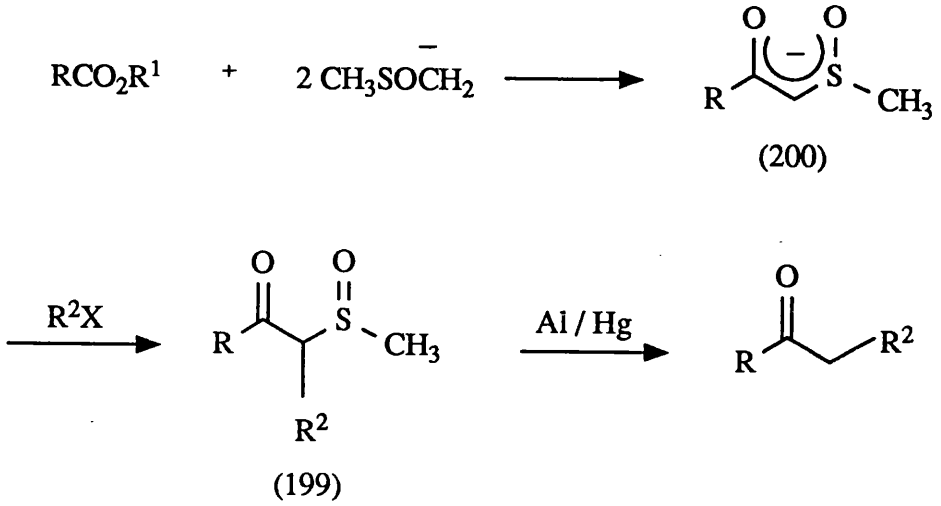
(169a) (198)

(170)

Scheme 65

Two equivalents of methyl lithium were required as the first equivalent would simply deprotonate the acidic carbazole NH group.

An efficient method of preparing ketones from carboxylic esters has been developed by Corey and co-workers[146]. This method involves attack on the carboxylic ester by the methylsulfinyl anion ($CH_3SOCH_2^-$) to form the β-keto sulfoxide (199).Subsequent reduction of this function, by aluminium amalgam gives the ketone. (Scheme 66).

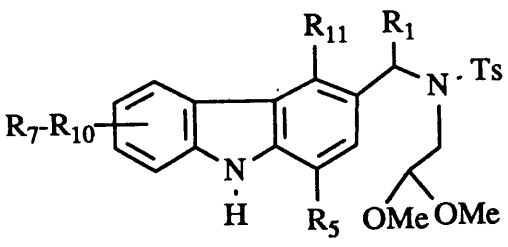


Scheme 66

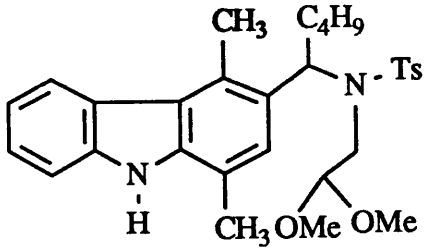
Two equivalents of the methyl sulfinyl anion are needed as the second molecule of the anion deprotonates the acidic proton α- to the carbonyl in the β-keto sulfoxide, in preference to attacking the ester.

As described in Scheme 66, the intermediate (200) can either be quenched by water or by an alkyl halide to give the methyl ketone or an alkyl ketone respectively.

This would be a useful method for introducing C-1 substituents in our pyridocarbazole synthetic route. If, however, both C-1 and C-11 are substituted then problems may arise, as *peri* interactions between the two groups could prevent the amine (163) from obtaining the required conformation for cyclisation.



(163)



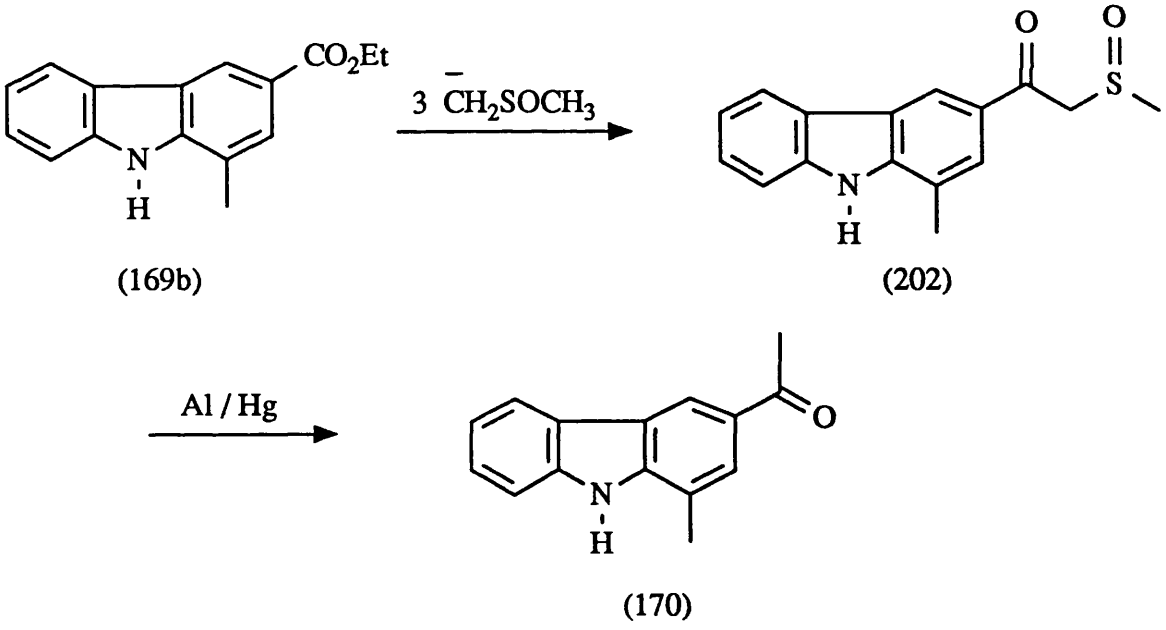
(201)

For example, Sainsbury and Smith[147] recently attempted to prepare

1-butylellipticine but failed to effect the final cyclisation of the intermediate (201).

The β-keto sulfoxide (202) was prepared in 72% yield by reaction of the ester (169b) with three molecular equivalents of the methylsulfinyl anion, followed by an acidic work up. It should be noted that, an extra equivalent of the methylsulfinyl anion was needed due to the acidic nature of the carbazole NH.

The β-keto sulfoxide (202) was reduced to the ketone (170) by the aluminium amalgam method[146] in 70% yield. (Scheme 67).



(169b) (202) (170)

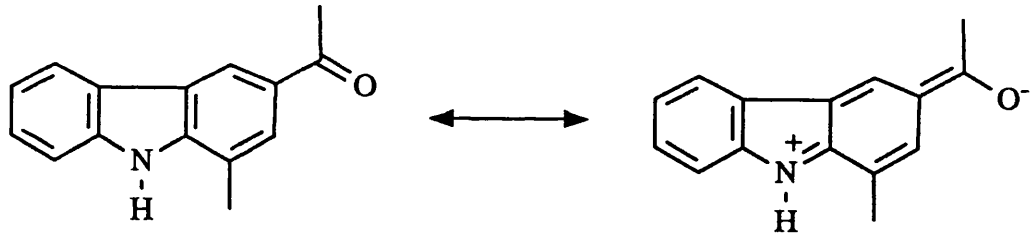
Scheme 67

We were now in a position where the ketone (170) could be synthesised in 71% yield (for the 5 steps from gramine and ketone (165b), on large scale) and next its elaboration to olivacine (2) was studied.

Narasimham and Gokhale reported[65] converting the ketone (170) to olivacine (2) in poor yields (Scheme 47), despite stating that the tosyl deriative (172) was successfully cyclised to olivacine (2) in 65% yield.

In our hands, reaction between the ketone (170) and aminoacetaldehyde dimethylacetal proved unsuccessful. Various conditions were employed, including the use of Dean-Stark apparatus and activated molecular sieves, to try and drive the condensation in the forward sense by removing product water. However, monitoring of the reaction by i.r. spectroscopy showed little or no reaction to have occurred. This was supported by ^{1}H n.m.r. spectroscopic analysis.

The ketone (170) is a vinylogous amide and this factor can explain its lack of reactivity. (Scheme 68).



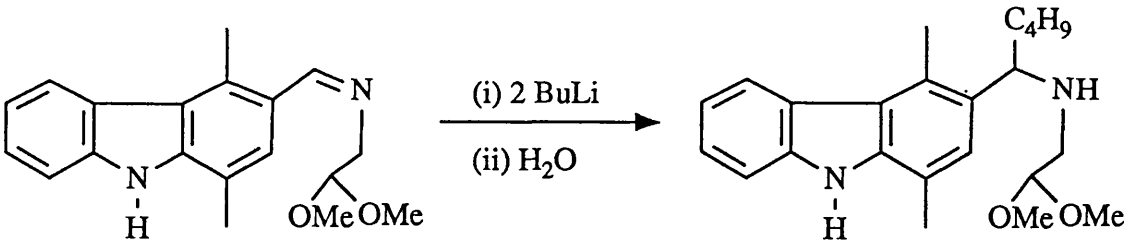
(170)

Scheme 68

Indeed, the infra red stretching frequency of the carbonyl functionality of compound (170) lies at 1650 cm^{-1}, a value more characteristic of an amide than a ketone.

Recent work in our group[147] has shown that imines of the type (203) can be successfully alkylated.

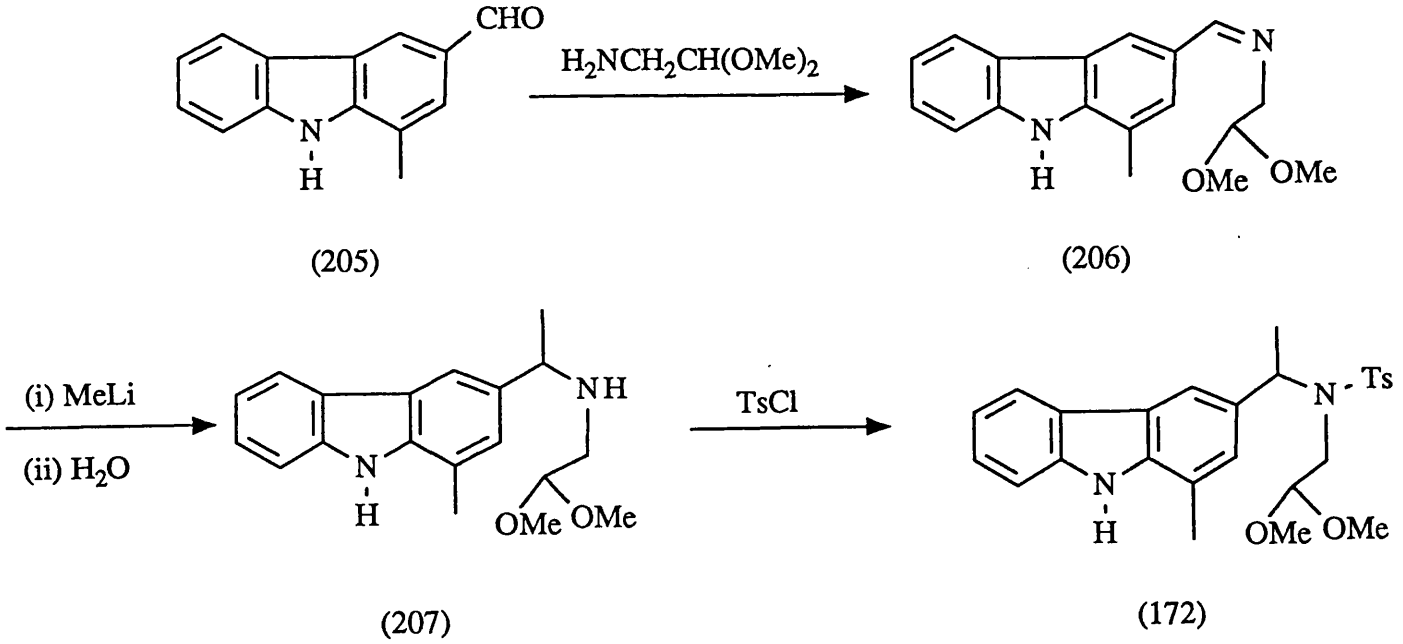
The imine (203) was treated with 2 equivalents of butyl lithium to yield the amine (204) after aqueous work up. (Scheme 69).



(203) (204)

Scheme 69

Therefore, a method of avoiding the poor reactivity of the methyl ketone (170) would be to react the more reactive aldehyde (205) and methylate the resulting imine (206). (Scheme 70).



(205) (206)

(207) (172)

Scheme 70

This method would not add an extra step to the synthesis as alkylation of the imine (206) gives the same product,amine (207),as reduction of the imine (171).(Scheme 47).

The aldehyde (205) was obtained in 94% yield by reduction of the nitrile (169a)

with diisobutyl almuminium hydride (DiBAL) and acidic hydrolysis of the intermediate imine.

Boiling a mixture of aminoacetaldehyde dimethylacetal and the aldehyde (205) in dry benzene, using Dean-Stark apparatus, for 4 hours yielded the required imine (206) in 96% yield.

The reaction was monitored by i.r. spectroscopy as t.l.c. analysis (using either silica or neutral alumina) causes hydrolyses of any product back to the aldehyde.

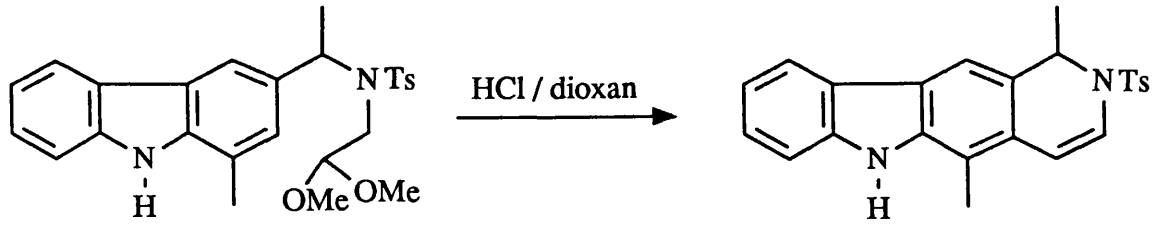
Loss of the C=O stretch at 1670 cm^{-1} was observed along with the emergence of the C=N stretch at 1635 cm^{-1}.

Treatment of the imine (206) with 2.2 equivalents of methyllithium yielded the amine (207), in 65% yield, after aqueous work up. Standard conditions (tosyl chloride/Na_2CO_3/THF/H_2O)[63] were employed to convert (207) to its tosyl derivative (172) in 84% yield.

Narasimham and Gokhale[65] reported the synthesis of olivacine (2), from the sulphonamide (172), by heating it in dioxane with aqueous hydrochloric acid. It was noted, to achieve good yields, that the water content must be reduced.

In our hands, similar conditions did not yield olivacine. The only identifiable product obtained, even after prolonged heating for 48h, was 1,2-dihydro-1,5-dimethyl-2-tosylpyrido[4,3-*b*]carbazole (208). Optimum conditions of heating for 6 hours produced this compound in 45% yield. (Scheme 71).

Decoupling and n.O.e. experiments were carried out on this product to authenticate its structure as (208).



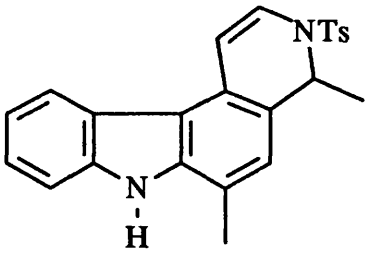
(172) (208)

Scheme 71

Decouplings on (208)

RESONANCE IRRADIATED (δ)	DECOUPLING EFFECT
6 · 8 ppm TsNC<u>H</u>=CH	6 ·3 ppm d x d → d , J = 3 Hz
6 · 3 ppm TsNCH=C<u>H</u>	6 · 8 ppm d x d → d , J = 2 ·5 Hz
5 ·4 ppm CH_3C<u>H</u>NTs	1 ·4 ppm d → s
1 ·4 ppm $C\underline{H}_3$CHNTs	5 ·4 ppm m→d , J = 1 Hz

In the n.O.e. experiment, when the C-5 $C\underline{H}_3$ singlet at 2.45 ppm was irradiated, an enhancement of 14% for the C-4 olefinic proton at 6.3 ppm plus a 6% enhancement for the N-H proton at 8.0 ppm were observed.(Spectrum Two)

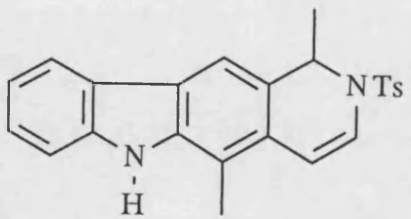


(209)

Thus, these experiments proved the structure to be (208) and not the alternative

n.O.e. experiment on (208)

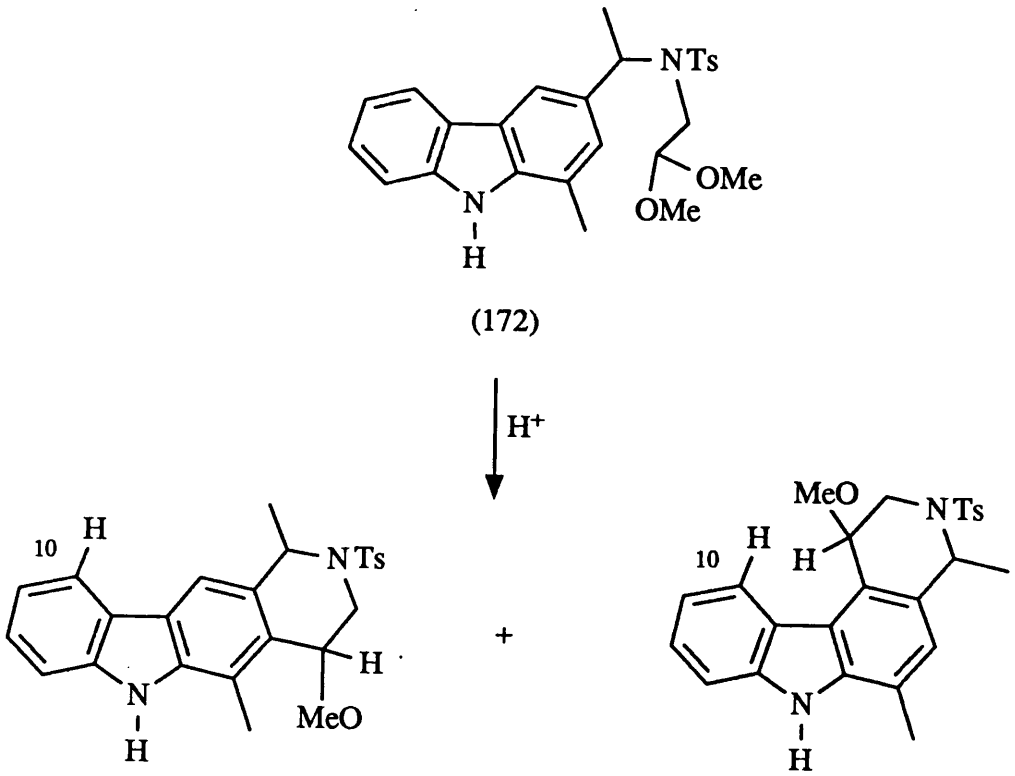
Spectrum Two



isomer (209).

This type of intermediate has been isolated previously in studies on ellipticines.[62,63]

Literature precedent[66,137] and models, however, suggest that formation of the angular isomer is not precluded, but we did not detect it, and a possible reason is that steric hindrance occurs in the necessary intermediate. For example, as carbazoles are curved structures, the C-10 hydrogen could interfere in the formation of species (211). (Scheme 72).



(172)

(210)

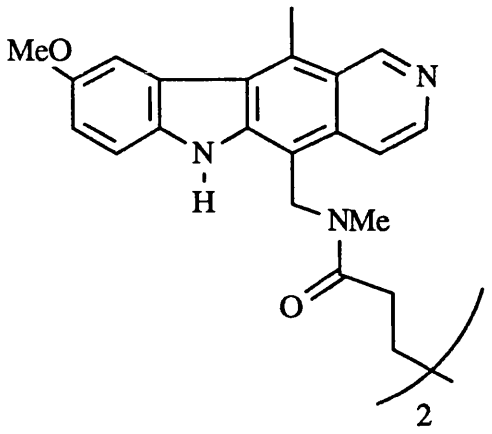
(211)

Scheme 72

Having successfully completed the model study, an attempt to synthesise functionalised 6H- pyrido[4,3-*b*]carbazoles was undertaken.

As described earlier (Scheme 46), a suitably substituted gramine derivative (157) and ketone (156) are required as the starting materials for this synthesis.

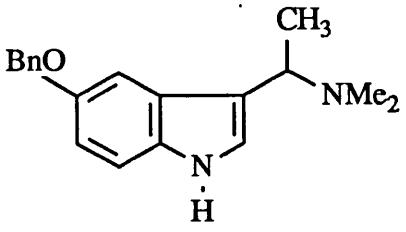
Another worker in our group[148] had recently obtained encouraging biological results for the dimer (212). Hence, we decided to initially concentrate our efforts towards 5-substituted ellipticines.



(212)

The previous worker[148] encountered difficulty in O-demethylating the 9-methoxylated ellipticine unit, so we considered that a benzyl function would be a better protecting group for the 9-hydroxy of ellipticine. This group could then easily be removed by hydrogenolysis at the end of the synthesis.

The required gramine is 1-(5-benzyloxy-3-indolyl)-*N*,*N*-dimethylaminoethane (213).

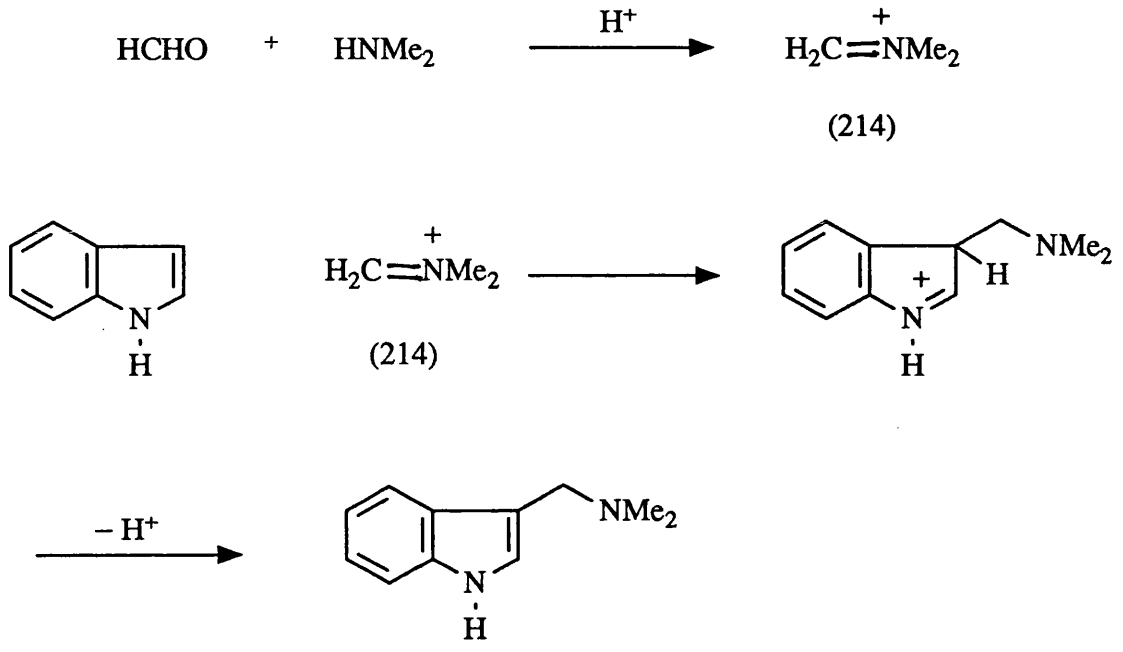


Bn = $C_6H_5CH_2$-

(213)

Gramine (166) is normally synthesised by the Mannich reaction.[150]

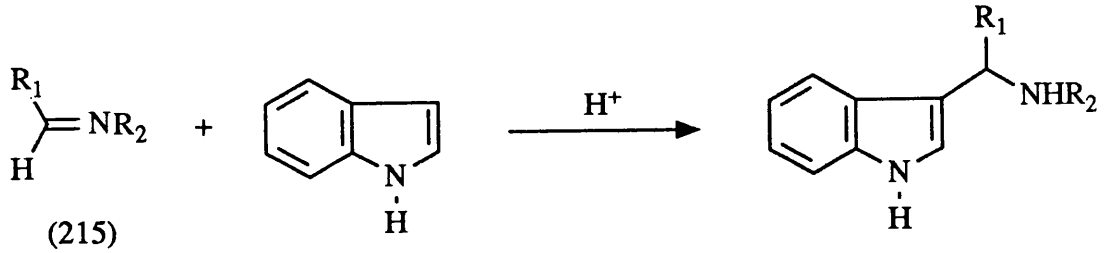
Initially, an iminium species (214) is formed which is then attacked by indole, acting as an enamine, to form the so-called Mannich base (166). (Scheme 74).



(166)

Scheme 74

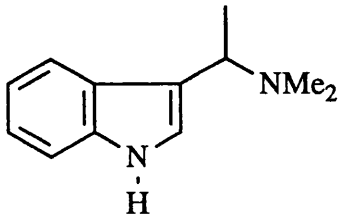
Attempts to use aldehydes other than formaldehyde to form Mannich bases have met with limited success, partly due to the reduced activity of the carbonyl species. However, α-substituted indole-3-methylamines of the Mannich type have been obtained[151,152] by the addition of indoles to preformed aldimines (215) in the presence of an acid catalyst, usually glacial acetic acid. (Scheme 75).



(215)

Scheme 75

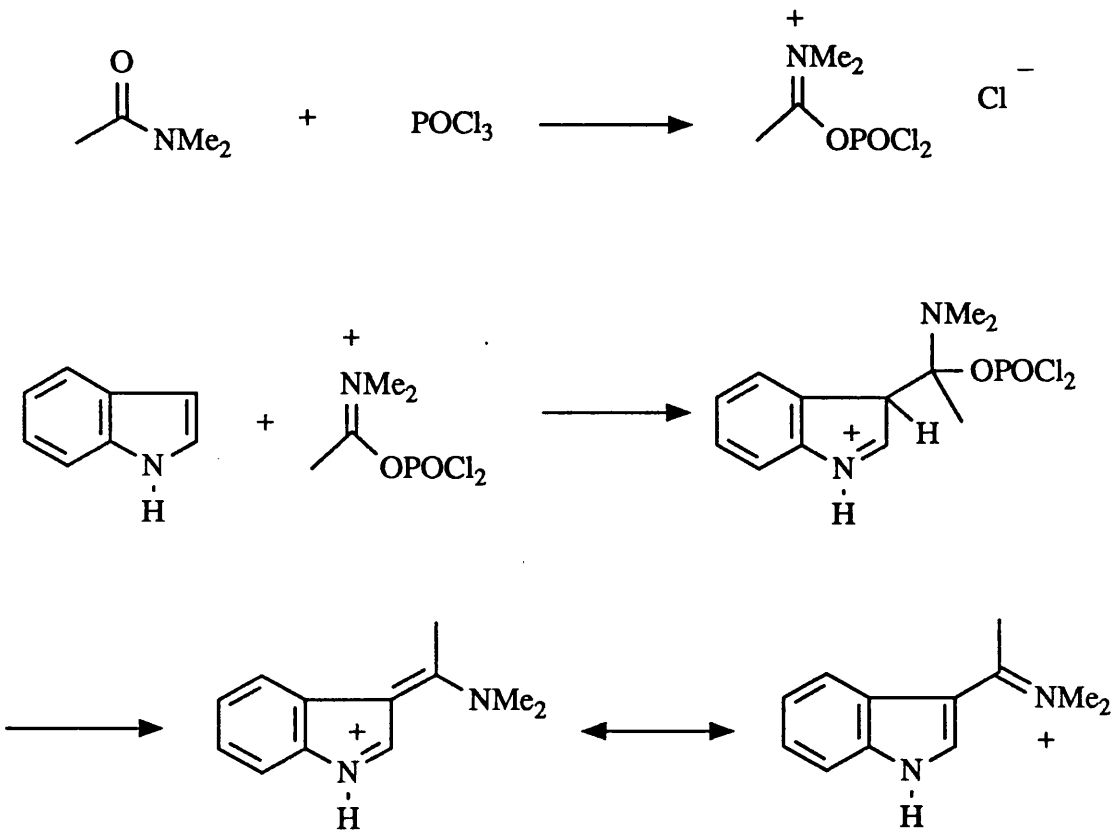
A search of the literature revealed that 1-(3-indolyl)-*N,N*-dimethylaminoethane (216) had been prepared by Le Goffic and co-workers by two methods.[149]



(216)

The first involves a standard Mannich reaction. Thus, indole was stirred in a mixture of dimethylamine hydrochloride, potassium carbonate, acetic acid and acetaldehyde at 4°C for 5 days to give the Mannich base (216) in 59% yield.

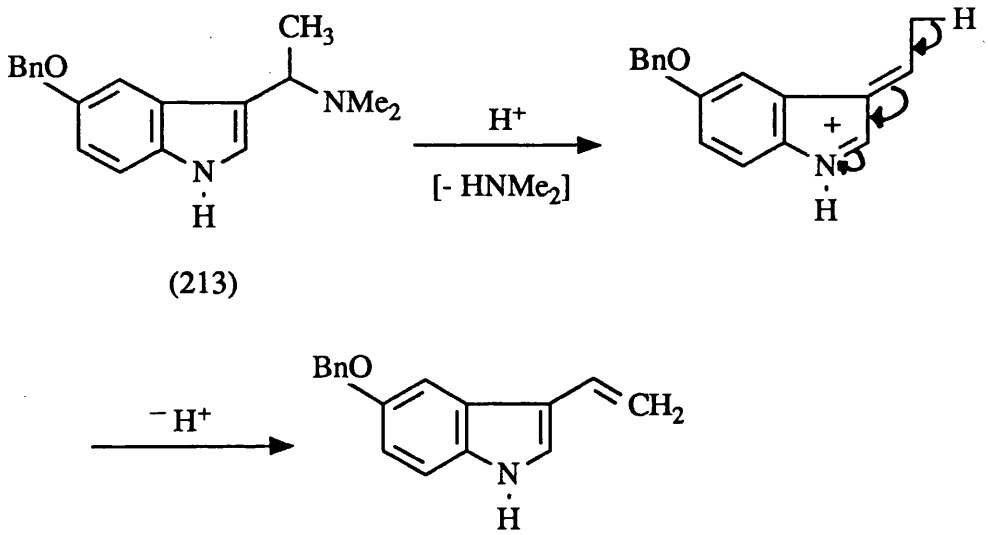
In the second approach, an iminium species, formed by a Vilsmeier-Haack reaction[153], was attacked by indole (Scheme 76). Reduction of the intermediate (217), with sodium borohydride, produced the gramine (216) in 65% overall yield. (Scheme 76).



(217)

Scheme 76

Both these procedures were applied to the synthesis of the 5-benzyloxy derivative (213). The reactions were monitored by t.l.c. analysis and proceeded quite smoothly. However, isolation of the pure compound was very difficult. The product was a viscous oil and attempts to crystallise the compound by trituration with various solvents failed. When heated in these solvents, the odour of dimethylamine was detected. Thus indicating that the vinyl indole (218) was formed by decomposition of the gramine (213). However, this product (218) was not detected so presumably it readily polymerises. (Scheme 77).



Scheme 77

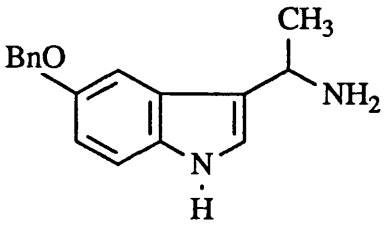
The β-hydrogen available in the α-methyl group of the Mannich base (213) allows this transformation to proceed. As gramine (166) does not have an available β-hydrogen, it is more stable.

In view of our results, we were surprised to read that the gramine (216) was a stable crystalline solid.[149] Presumably, the instability of our benzyloxy gramine (213) is due to the electron donating effect of the oxygen substituent which promotes the

elimination of dimethylamine from the molecule.

In view of this, the crude benzyloxy gramine (213) was always prepared just prior to use.

Whilst attempting to reduce the intermediate (217), an interesting result was obtained. Before the addition of sodium borohydride, the reaction mixture was basified with 0.88 ammonia. However, transamination must have occurred, as the product isolated was 1-amino-1-(5-benzyloxy-3-indolyl)ethane (219).



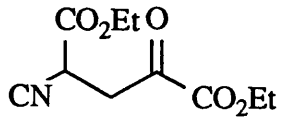
(219)

The product (219) was a stable solid and could be used in subsequent condensation reactions with the required ketones (156).

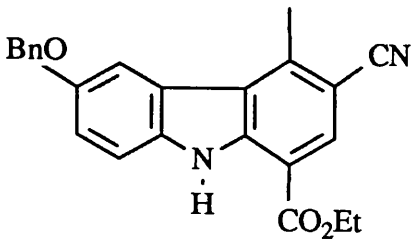
Considering the synthesis of a suitably substituted ketone (156), we concluded that an ester functionality as R_5 (Scheme 46) would be useful. A series of transformations could then be applied to it, in order to vary the nature of the side chain of the final ellipticine.

Hence, the synthesis of the ketone (220) was undertaken, with a view to its elaboration to the carbazole (221).

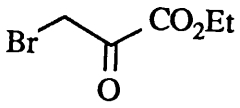
Following our earlier procedure, we attempted to react the anion of ethyl cyanoacetate with ethyl bromopyruvate (222).



(220)



(221)



(222)

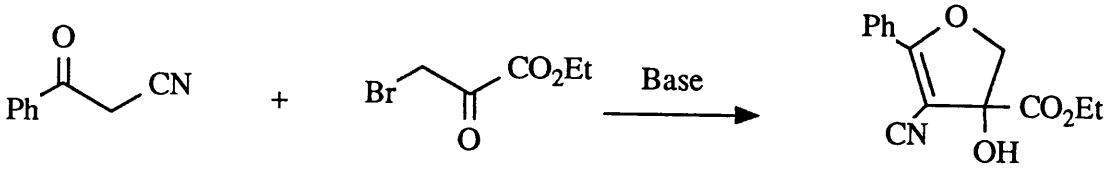
Unfortunately, the reaction gave a complex mixture of products. We assumed that the anion was indiscriminate in its reactivity and attacked the keto function of the pyruvate as well as coupling through the displacement of bromide ion, as required.

A similar reaction was carried out with the anion of malononitrile, but again, a complex mixture was obtained.

Shortly after we carried out this work, a report by Mansour[154] confirmed that such a reaction does indeed occur with this type of substrate and nucleophiles.

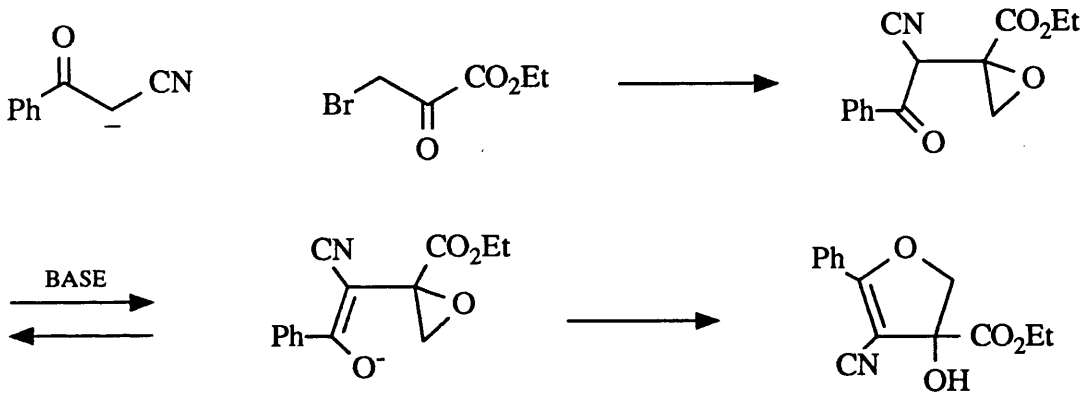
Mansour, in an attempt to condense benzoylacetonitrile (223) with ethyl bromopyruvate (222), isolated 4-cyano-3-ethoxycarbonyl-2,3-dihydro-3-hydroxy-5-phenylfuran (224) in 57% yield. (Scheme 78).

Formation of the dihydrofuran (224) was explained by nucleophilic addition of the anion of (223) to the reactive carbonyl group of the pyruvate. This addition is followed by either direct displacment of bromide ion or, more likely, through the intermediacy of the epoxide (225). (Scheme 79).



(223) (222) (224)

Scheme 78



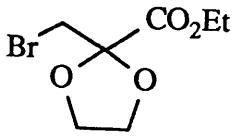
(225) (224)

Scheme 79

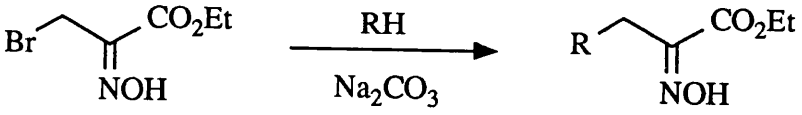
Protection of the ketone function of ethyl bromopyruvate (222) was now considered necessary.

The dioxolane (226) was obtained in 47% yield by reaction of ethyl bromopyruvate (222) with ethylene glycol and *p*-toluene sulphonic acid in boiling benzene.

However, attempted reactions between the anion of ethyl cyanoacetate and the dioxolane (226), even under severe conditions, failed. This lack of reactivity is due to the *neo*-pentyl like structure of the dioxolane (226), which provides steric interference towards nucleophilic attack.[155]



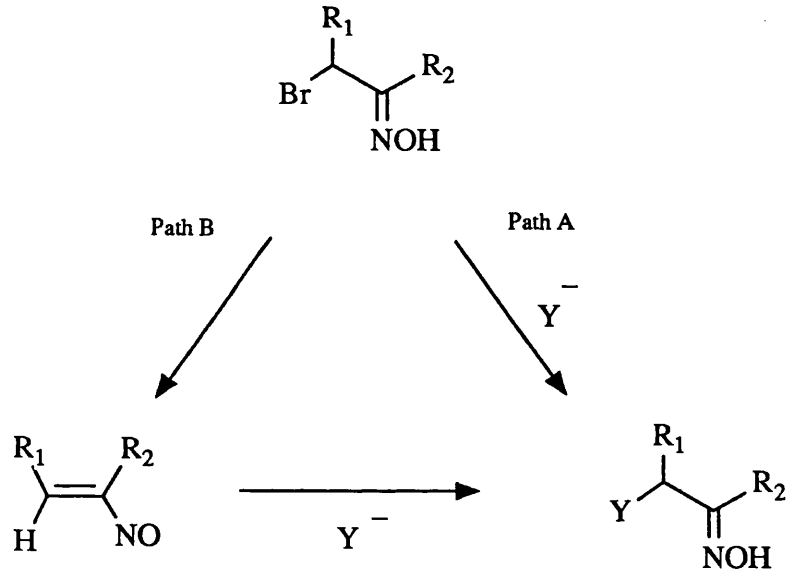
(226)



(227)

R = 3 - Indolyl ; 2 - Pyrrolyl ; $PhCH_2S$; $(EtO_2C)CH$.

Scheme 80



(228)

Scheme 81

A search of the literature revealed that Gilchrist and his co-workers[156] have been successful in reacting ethyl 3-bromo-2-hydroxyiminopropanoate (227) with a range of nucleophiles in the presence of sodium carbonate. (Scheme 80).

Such reactions can, in principle, take place either by direct nucleophilic displacement or by elimination of hydrogen halide, followed by addition of the nucleophile. (Scheme 81).

The elimination-addition mechanism (path B) can be brought about by use of an

external base, or, if the nucleophile is sufficiently basic, by the nucleophile itself.

Evidence for an elimination-addition mechanism in such reactions is provided by the isolation or detection of intermediate nitrosoalkenes (228).[158]

A typical procedure for these reactions ivolves stirring the bromoester with an excess (2-5 molecular equivalents) of the substrate, in the presence of sodium carbonate, in dichloromethane.

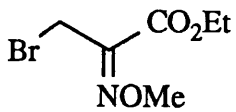
The bromoester (227) is a colourless, crystalline solid and was prepared by the method of Ottenheijm *et al.*[157]

However, when we attempted the standard reaction between the bromoester (227) and ethyl cyanoacetate, no identifiable product could be isolated.

The ^{1}H n.m.r. spectrum of the crude product showed that a complex mixture had formed, none of which contained an oxime function.

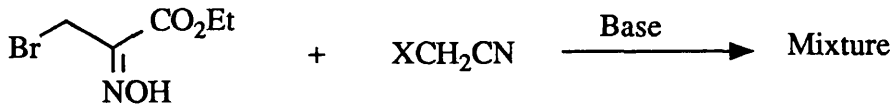
Alternative methods of generating the anion of ethyl cyanoacetate with different bases in various solvents and adding it to the bromoester gave similar negative results. (These results are summarised in Table 1).

Noting the loss of the oxime proton signal in the ^{1}H n.m.r. spectrum we envisaged that the first equivalent of the ethyl cyanoacetate anion was deprotonating the oxime and then cyclisation reactions were occurring.



(229)

Table One



(227)

X	Base	Conditions
CO_2Et	Na_2CO_3	CH_2Cl_2 / 24h
CN	Na_2CO_3	CH_2Cl_2 / 16h
CO_2Et	$Na^+ {}^-OEt$	EtOH / 1h
CO_2Et	NaH	DMF / 5 min
CO_2Et	$Na^+ {}^-OEt$	EtOH / 5 °C / 5 min
CO_2Et	$n\text{-}Bu_4{}^+ {}^-OH$	CH_2Cl_2 / H_2O / 3 min

With this in mind, we considered preparing the methoxime derivative of ethyl bromopyruvate (229), and attempting nucleophilic substitution of the bromide.

Ethyl 3-bromo-2-methoxyiminopropanoate (229) had not previously been reported, but was efficiently obtained by adaption of the method used for the synthesis of the hydroxyimino ester (227).[157]

Thus, a mixture of methoxyamine hydrochloride, ethyl bromopyruvate, chloroform and methanol was stirred vigorously at ambient temperature for 16 hours. After work-up, the methoxyimino ester (229) was obtained as a colourless oil in 88% yield.

When the methoxyimino ester (229) was treated with the anion of ethyl cyanoacetate in DMF, two products were detected by t.l.c. (consumption of the starting methoxyimino ester (229) was complete in less than 5 minutes at ambient temperature.).

Separation of the two products by column chromatography and subsequent characterisation revealed their structures to be the expected monoalkylated product (230) and the dialkylated product (231). (Scheme 82).

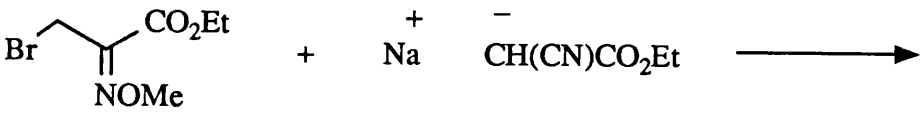
The yields of (230) and (231) were 26% and 60% respectively. After chromatography, the monoalkylated product (230) was found to be contaminated by ethyl cyanoacetate reformed by deprotonation of the product (230). Pure product (230) could be obtained by bulb to bulb distillation.

Attempts to try and optimise the yield of the monoalkylated product, by varying the conditions of the reaction were made. However, no real success was attained.

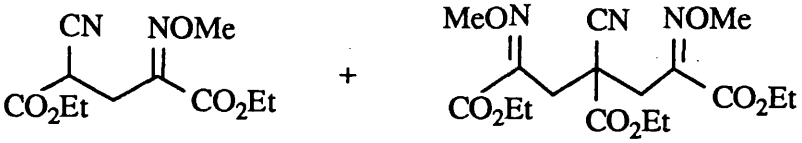
The best yield of the monoalkylated product (230) obtained was 51%. This

result was achieved by stirring ethyl cyanoacetate and the bromoester (229) in dichloromethane/water with 1.5 molecular equivalents of the phase transfer catalyst, tetra-n-butylammonium hydroxide, for 30 minutes.

(All the experiments tried are summarised in Table 2.)



(229)



(230) (231)

Scheme 82

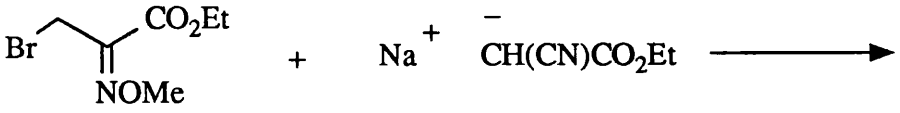
Reaction of the bromoester (229) with the anion of malononitrile was carried out, but again, a mixture of the monoalkylated product (232, 29% yield) and the dialkylated product (233, 54% yield) was obtained. (Scheme 83).

Having obtained some of the methoxime (230), we now attempted to convert it to the required ketone (220).

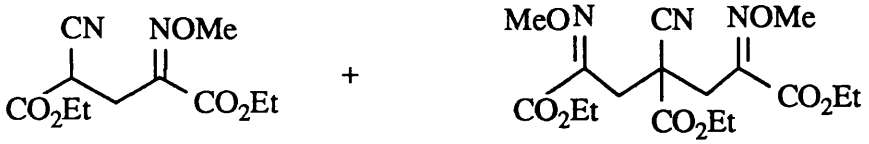
Oximes are typically converted to their respective ketones by reduction with titanium(III)[159] or thallium(III)[160] compounds and subsequent acid hydrolysis.

In our hands, however, treating the methoxime (230) with either titanium(III) chloride or thallium trinitrate at room temperature did not lead to the desired ketone

Table Two



(229)

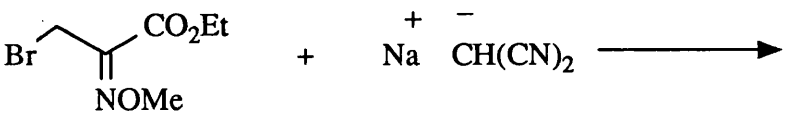


(230) (231)

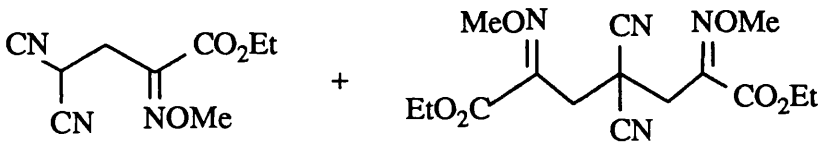
Base	Conditions	Yield (230)	Yield (231)
NaH	DMF / 0 °C / 5 min	26%	60%
$Na^{+-}OEt$	EtOH / 0 °C / 1h	30%	52%
$n\text{-}Bu_4N^{+-}OH$	CH_2Cl_2 / H_2O / 30 min	51%	41%
NaH	THF / −78 → 0 °C / 4h	23%	54%
$n\text{-}Bu_4N^{+-}F$	CH_2Cl_2 / H_2O / THF / 48h	24%	47%
$n\text{-}Bu_4N^{+-}F$	DMF / 10 min	24%	49%
$n\text{-}Bu_4N^{+-}OH$ (1.5 equivs.)	CH_2Cl_2 / H_2O / 6 days	52%	30%

(220).

If the reaction mixture was heated, consumption of the starting material was observed by t.l.c. analysis, but a complex product resulted(these results are summarised in Table 3.).



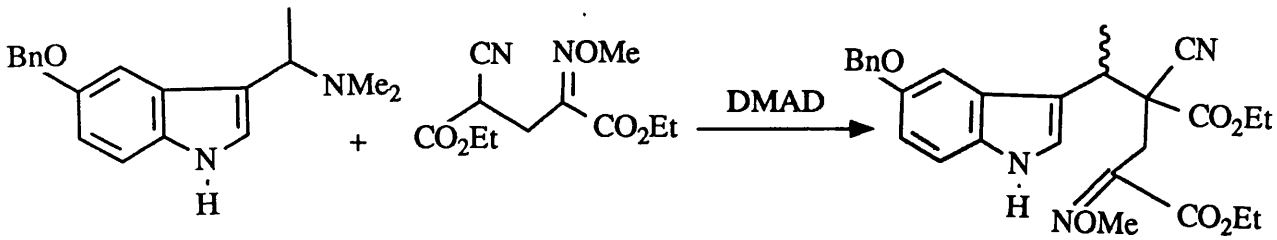
(229)



(232) (233)

Scheme 83

Despite these disappointing results, it was decided to condense the methoxime (230) with the gramine (213) to yield the indole (234). (Scheme 84).

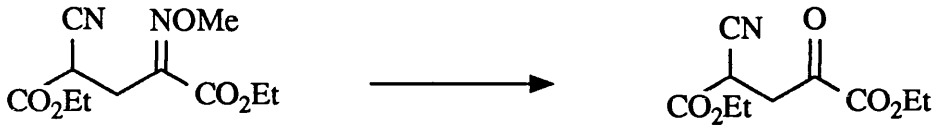


(213) (230) (234)

Scheme 84

This condensation was achieved in 41% yield by stirring a mixture of the methoxime (230), the gramine (213) and dimethyl acetylenedicarboxylate (DMAD) in dry THF for 16 hours.

Table Three

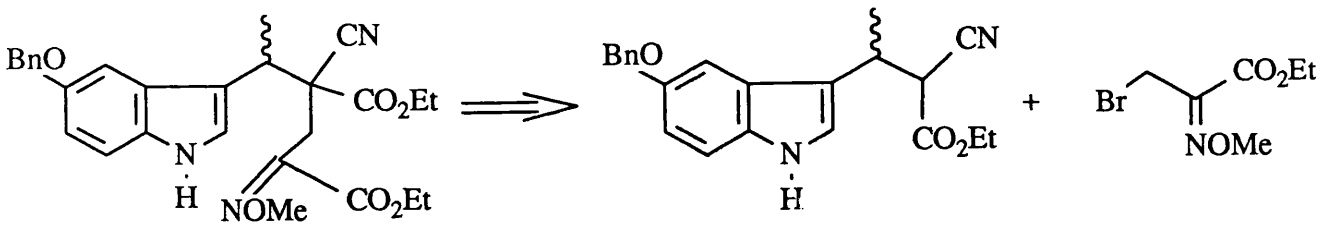


(230) (220)

Reagents	Conditions	Result
$TiCl_3$ / HCl	H_2O / AcOH / NH_4OAc Dioxane / 48h	No Reaction
$TiCl_3$ / HCl / $ZnCl_2$	DMF / AcOH / H_2O / 16h	No Reaction
$TiCl_3$ / HCl / $ZnCl_2$	DMF / AcOH / H_2O 100 °C / 90 min	Complex Product
$TiCl_3$	DMF / AcOH / H_2O NH_4OAc / 60 °C / 2h	No Reaction
$TiCl_3$	Dioxane / AcOH / H_2O NH_4OAc / 60 °C / 35h	Complex Product
$Tl(NO_3)_3$	Methanol / 2h	No Reaction

The indole (234) was obtained as a light beige oil. ^{1}H n.m.r. analysis proved the product to be an equal mixture of two diastereomers. Attempts to separate the two compounds by crystallisation failed and the mixture was used in subsequent experiments.

Having synthesised the indole (234), we observed that another method was available for its synthesis. (Scheme 85).



(234) (235) (229)

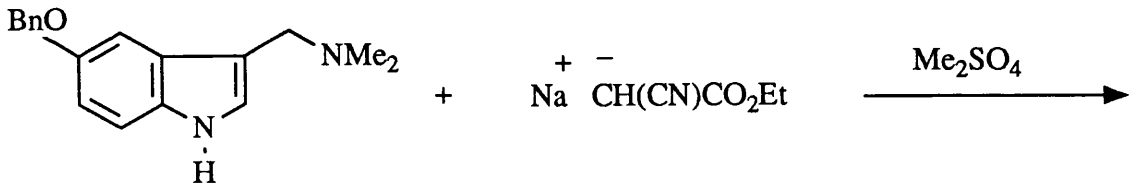
Scheme 85

Following the earlier procedure, we attempted to prepare the indole (235) by reacting the benzyloxy gramine (213) with ethyl cyanoacetate in the presence of DMAD in dry THF.

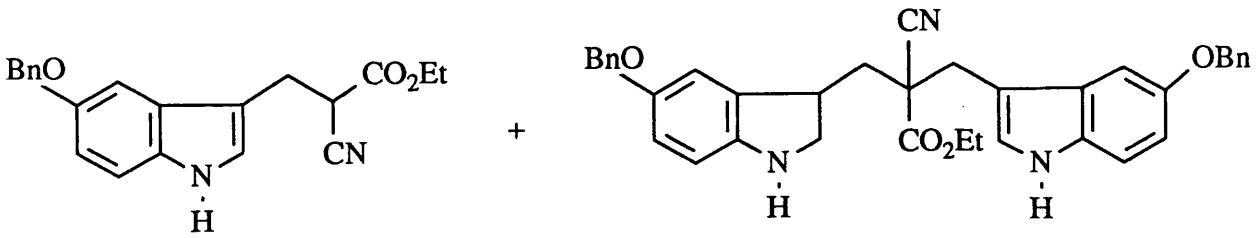
After column chromatography, the product of this reaction afforded the indole (235), as a mixture of two diastereomers, in 28% yield.

This disappointing result could not be improved and alternative methods for the preparation of this compound were considered.

To try and discover why the above reaction did not proceed cleanly, the anion of ethyl cyanoacetate was reacted with the methiosulphate salt of the gramine (236). (Scheme 86).



(236)



(237) (238)

Scheme 86

After column chromatography of the product, two compounds were isolated. These proved to be the expected product (237), in 24% yield, along with the dialkylated product (238), in 47% yield. (The reaction between the gramine (236) and ethyl cyanoacetate in the presence of DMAD produced the indole (237) in 19% yield).

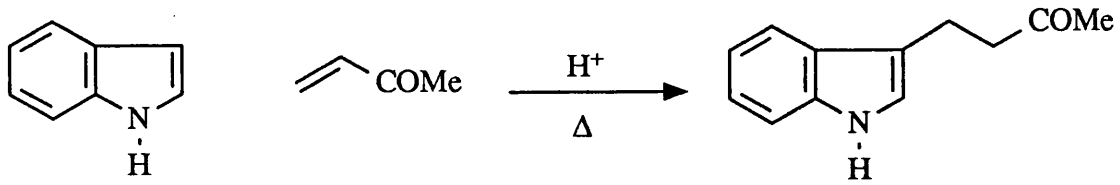
This was a disappointing result and the tendency for 'dialkylation' to occur is probably the reason why the DMAD reactions gave such poor yields for the preparation of indoles (235) and (237).

Not deterred by these results, a literature search was undertaken and we were encouraged by a recent publication by Jackson *et al.*[140] in which the reaction of indole and methyl vinyl ketone in the presence of montmorillonite clay (an acidic clay catalyst) in boiling dichloromethane is reported to yield the adduct (239). (Scheme 87).

The same reaction has also been reported by Szmuszkovicz[161] but using acetic

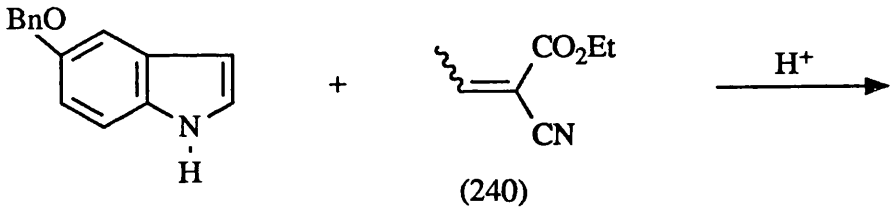
acid/acetic anhydride as the reaction medium.

We envisaged that the same reaction could be carried out with the α,β-unsaturated ester (240) and 5-benzyloxyindole to produce the desired indole (235). (Scheme 88).

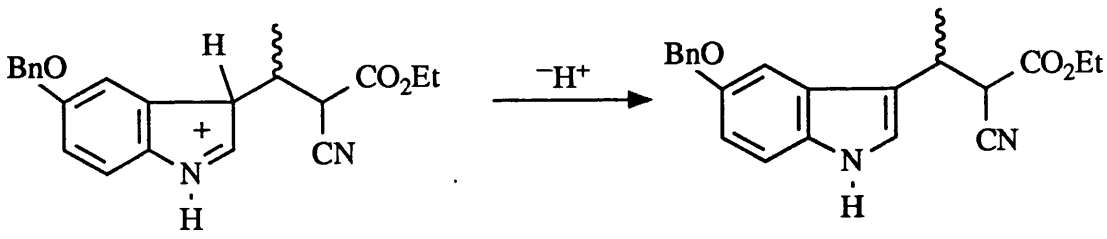


(239)

Scheme 87



(240)



(235)

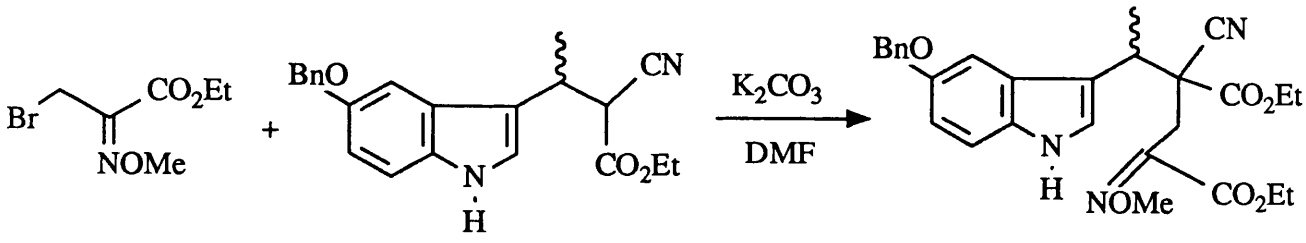
Scheme 88

The α,β-unsaturated ester (240) was prepared according to the method of Popp and Catala[162] in 38% yield,and when a mixture of 5-benzyloxy indole, ethyl 2-cyanobut-2-enoate (240) and montmorillonite clay was heated in boiling dichloromethane or toluene the required indole (235) was formed in 26% and 27% yield respectively. In each case, a significant amount of starting indole was recovered.

However, when we attempted the same reaction in a mixture of acetic acid and acetic anhydride, at 90°C for eight hours, total consumption of the starting indole occurred and now the desired indole (235) was isolated from the reaction product in 68% yield.

This compound was obtained as a light beige oil, and its ^1H n.m.r. spectrum indicated it to be a mixture of two diastereomers. Crystallisation from ethyl acetate/pet.ether gave a pure diastereomer in the form of colourless crystals. The diastereomeric mixture was used in subsequent experiments(alkylation of the pure diastereomer (235) gave the product (234) as a mixture of diastereomers-scrambling of one chiral centre having occurred through deprotonation).

Heating the indole (235) with bromoester (229) and potassium carbonate in dry DMF at 100°C gave the desired indole (234) in 74% yield. (Scheme 89).



(229) (235) (234)

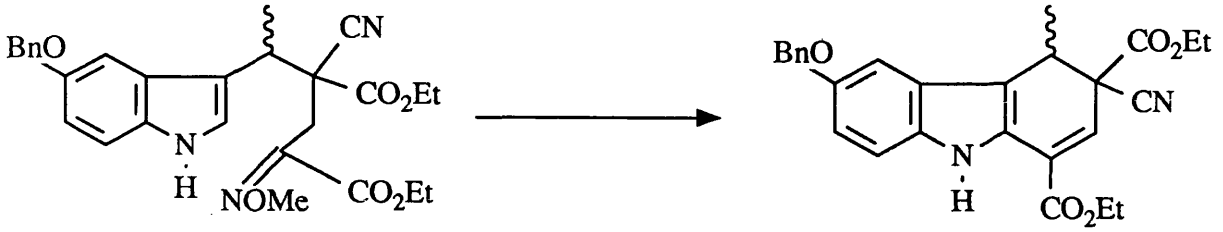
Scheme 89

We were now in a position to synthesise the intermediate indole (234), on large scale. Typically in 50% yield for the two steps from 5-benzyloxyindole.

We considered two possible ways of effecting the ring closure of indole (234) to the dihydrocarbazole (241). (Scheme 90).

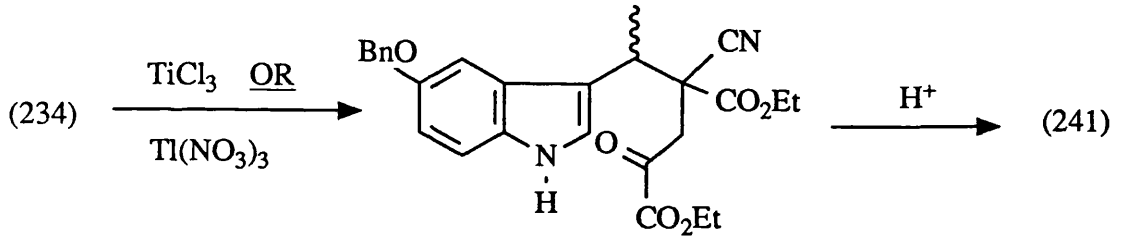
Initially we attempted to reduce and hydrolyse the methoxime to the β-keto

ester (242) and then to ring close this compound to the dihydrocarbazole in the presence of acid. (Scheme 91).



(234) (241)

Scheme 90



(242)

Scheme 91

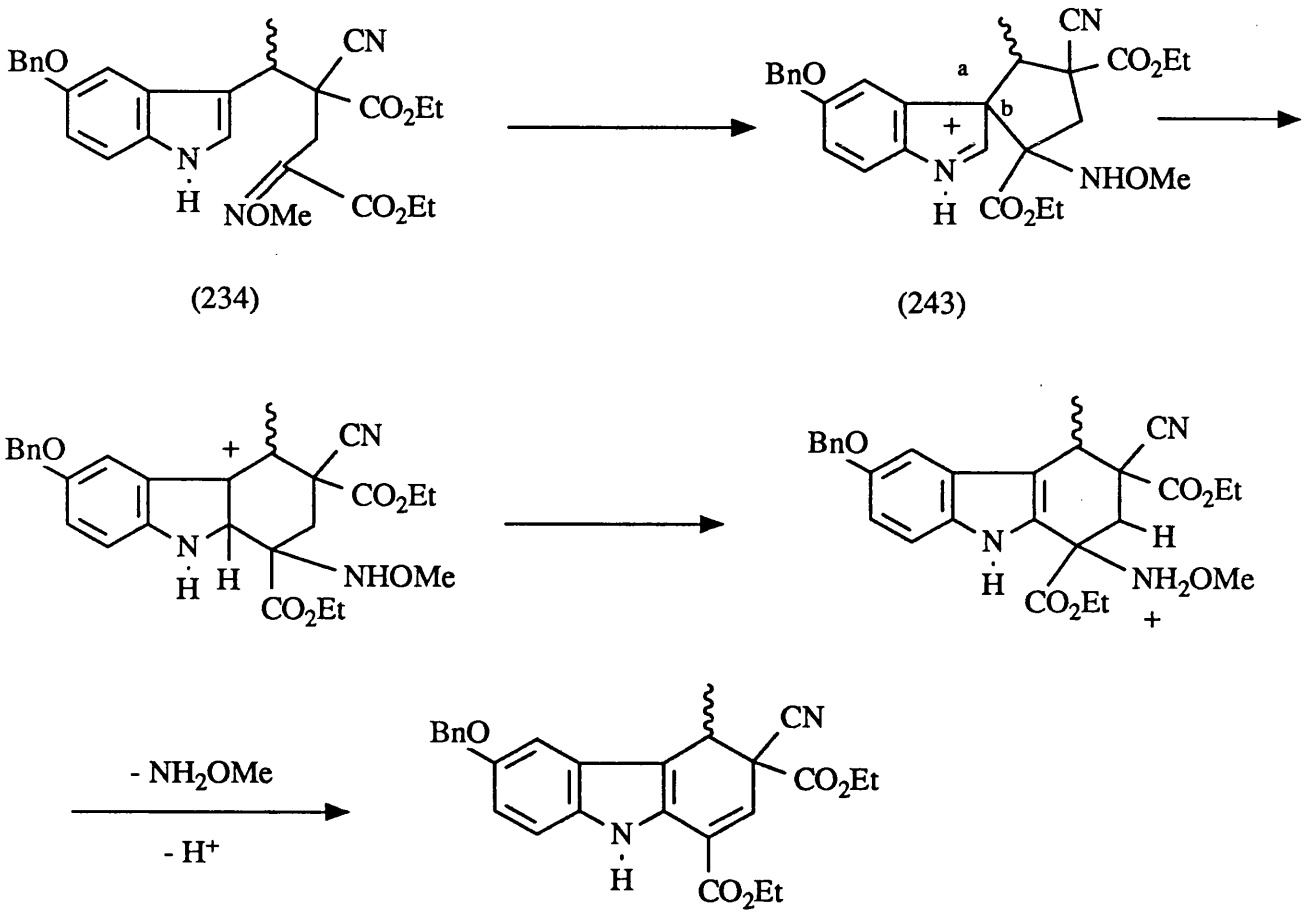
However, treatment of the methoxime (234) with either thallium(III) nitrate or titanium(III) chloride did not cause the required deprotection.

Alternatively, we considered that acidic conditions might induce the required ring closure by direct loss of methoxyammonia as indicated below. (Scheme 92).

The first conditions employed to attempt this transformation involved heating the methoxime (234) in refluxing 50% aqueous acetic acid. The reaction was monitored by t.l.c. analysis and the formation of a new, less polar product was observed.

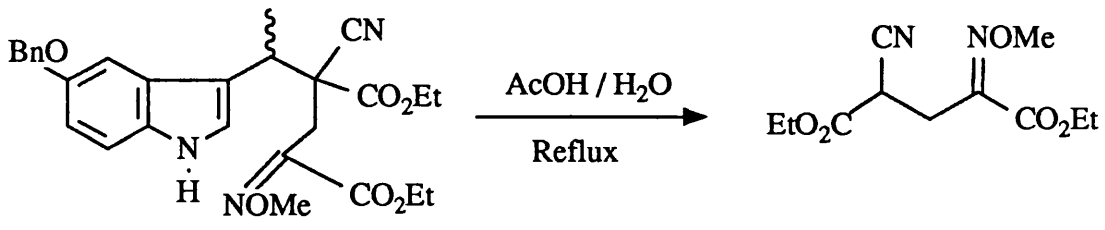
After 50 minutes, the reaction was worked up and the product purified by

column chromatography. However, the ^1H n.m.r. spectrum of the new product showed it to be the methoxime (230). (Scheme 93).



(234) (243) (241)

Scheme 92



(234) (230)

Scheme 93

We subsequently decided to avoid high temperatures to prevent this 'reverse'

reaction occurring.

However, treatment of the methoxime (234) with trifluoroacetic acid; aqueous trifluoroacetic acid; acetic acid or aqueous acetic acid at ambient temperature either gave no reaction or a complex product mixture. (These results are summarised in Table 4).

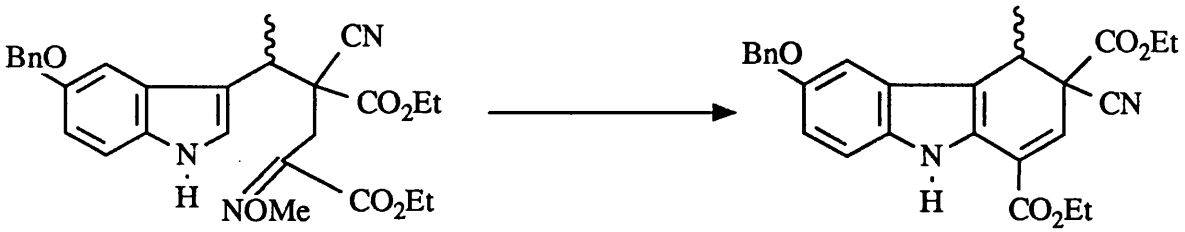
Partial success was achieved by stirring the methoxime (234) in dioxane saturated with hydrogen chloride. This procedure led to a mixture of products from which the required dihydrocarbazole (241) was isolated, as a mixture of two diastereomers, in 21% yield.

Similarly, when the methoxime (234) was treated with polyphosphate ester, in refluxing chloroform, a complex mixture was again obtained. Careful column chromatography afforded the required dihydrocarbazole (241) but only in 25% yield. N.O.e. experiments were carried out on this compound to authenticate its structure.If the product was the isomeric compound (244),an enhancement of the C-1 methyl signal at 1.52 ppm should have been observed when the N-H signal at 10.20 ppm was irradiated.However,as no enhancement was seen,the product was assumed to have the required structure (241).

The low yield of the dihydrocarbazole (241) was a very disappointing result and we concluded that one factor behind it is that there are two bonds, (a) and (b), in the presumed reaction intermediate (243) which may migrate. This would give rise to two products, either of which are able to react further. (Scheme 94).

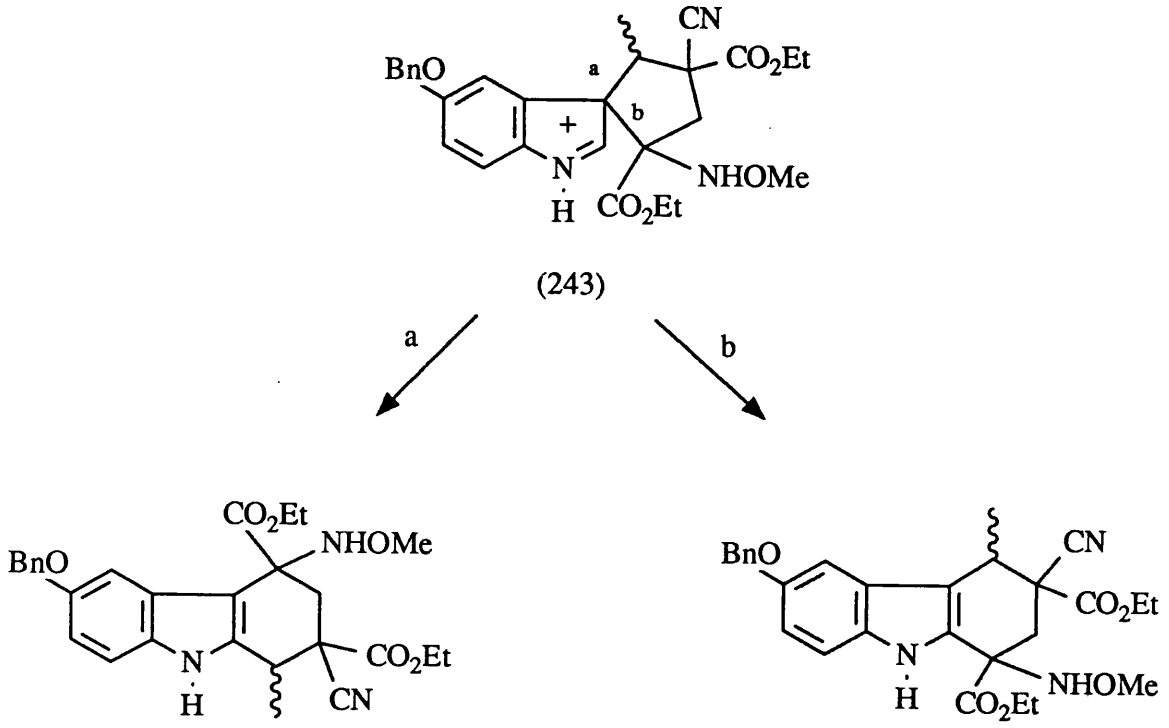
Migration of the correct bond, (b), should be promoted by electron release from the nitrogen.[139] However, in the intermediate (243), this effect may be offset by the electron withdrawing properties of the geminal ethoxycarbonyl function.

Table Four



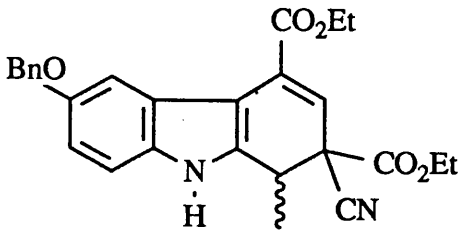
(234) (241)

Reagent	Conditions	Result
50% Aqueous AcOH	Reflux / 50 min	Mixture of (234) and (229)
CF_3CO_2H	30 min	Complex Product
50% Aqueous CF_3CO_2H	18h	Complex Product
$TiCl_3$	NH_4OAc / AcOH / H_2O DMF / 20h	No Reaction
$Tl(NO_3)_3$	Methanol / 30h	No Reaction
HCl	Dioxane / 36h	(241),21%
AcOH	5 days	No Reaction
50% Aqueous AcOH	5 days	No Reaction
Polyphosphate Ester	$CHCl_3$ / Reflux / 48h	(241),25%
HCl	50 °C / 21h	(241),7%
$H_2NCONHNH_2 \cdot HCl$	EtOH / H_2O / Reflux	No Reaction



Scheme 94

In order to confirm this view, extensive column chromatography was carried out to try and isolate the alternative dihydrocarbazole (244), but without success.

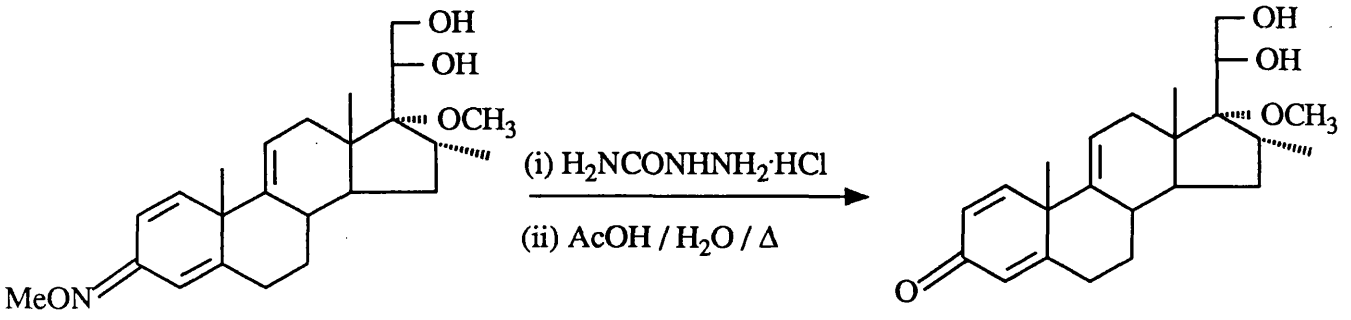


(244)

We were, however, able to obtain the required dihydrocarbazole (241) free from contaminants, but the ^{1}H n.m.r. spectrum of the crude reaction mixture showed the presence of at least six indole compounds.

A report by Fried and Nutile[163] described that the C-3 methoxime of the steroid

(245) proved to be extremely stable toward a number of acidic hydrolytic reagents. Eventually the free C-3 ketone (246) was obtained by conversion of the methoxime to the semicarbazone, followed by aqueous acetic acid hydrolysis. (Scheme 95).

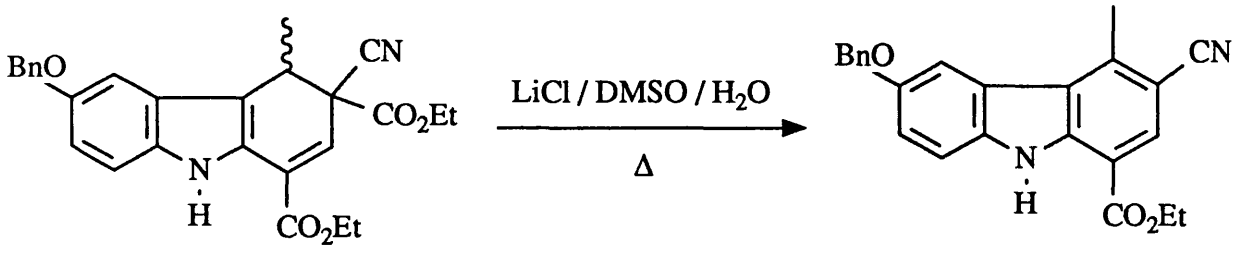


(245) (246)

Scheme 95

Heating our methoxime (234) with semicarbazide hydrochloride in water and ethanol proved no more successful than many other reagents and the starting material was again returned unchanged.

When the dihydrocarbazole (241) was heated with lithium chloride, water and DMSO at 100°C for 26 hours the required carbazole (221) was obtained in 45% yield. (Scheme 96).

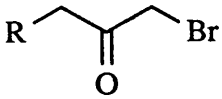


(241) (221)

Scheme 96

We now considered the worth of reducing the 1-ethoxycarbonyl function in the methoxime (234) prior to the ring closure. This would establish whether the electron withdrawing property of this group affects the cyclisation procedure. However, due to the presence of another ethoxycarbonyl function in the molecule (234)(geminal with the nitrile),problems of selective reduction were envisaged.

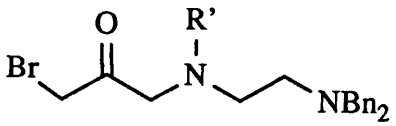
Also, presuming that elimination of methoxyamine (rather than water) might also be affecting the ring closure, we decided to synthesise a new synthon of general structure (247) specifically designed to avoid the difficulties cited above.



(247)

Due to the general insolubility of the ellipticine derivatives, we decided to synthesise a compound (247) where R was a group involving one or more amino groups as these could be converted into ammonium salts in the fully elaborated compound.

On this basis, the diamine (248) (R^1 = alkyl) was chosen, as this unit could eventually be deprotected, by hydrogenolysis, to give a primary amine.



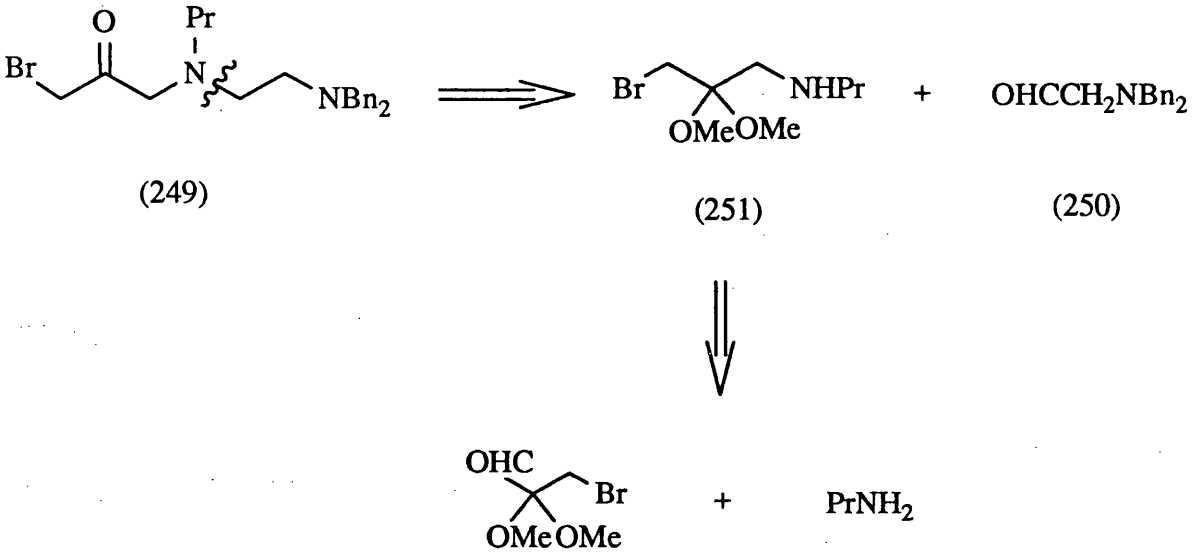
Bn=$C_6H_5CH_2$-

(248)

This primary amine would then be useful in the further elaboration of the side

chain in the final ellipticine or for the coupling of two ellipticine units *via* a diacid or dialdehyde. (Scheme 97).

Having reactive halo, keto and amino functions in this synthon (248) might present stability problems and the ketone function would have to be protected throughout the synthesis, as our retrosynthetic analysis describes. (Scheme 98).



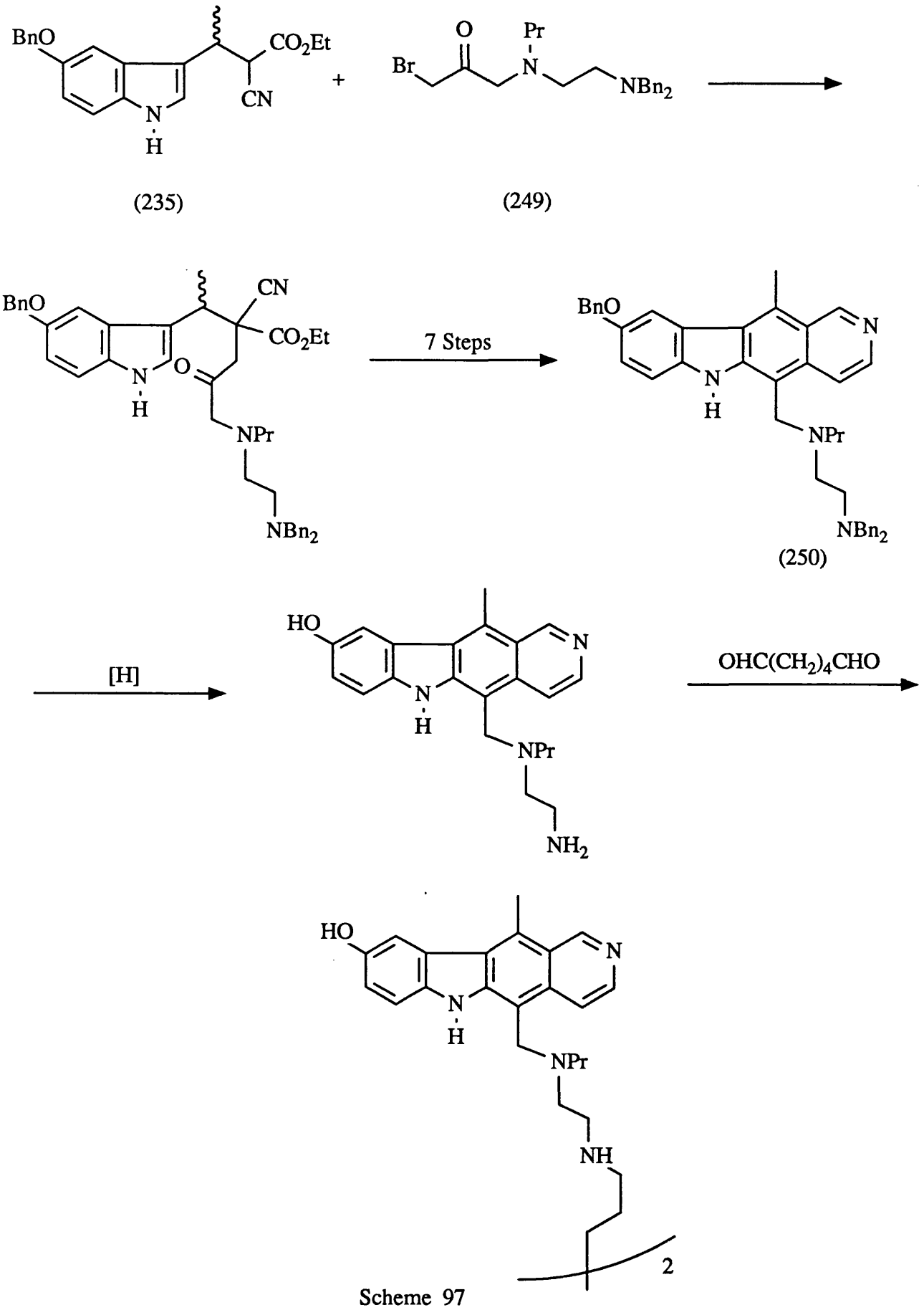
(249) (251) (250)

(252)

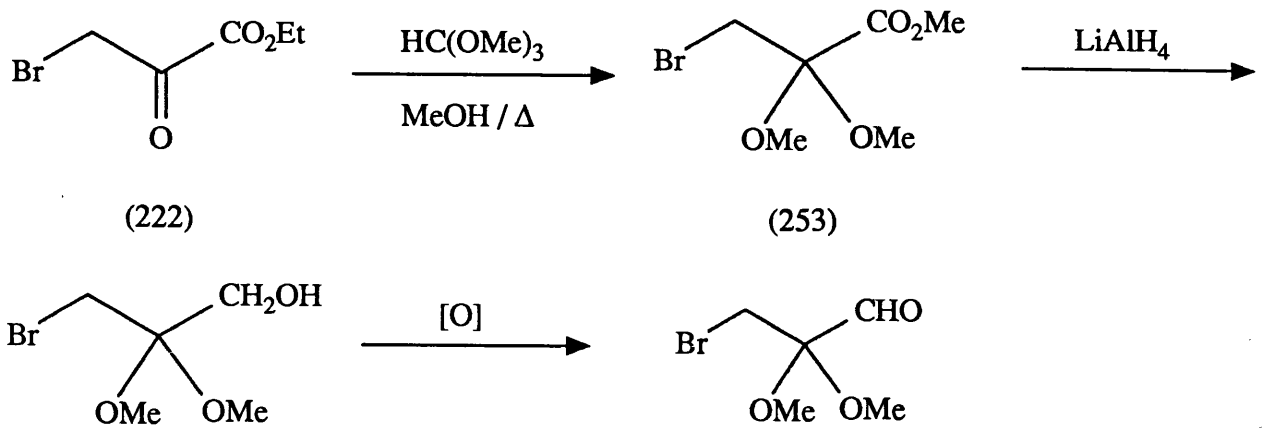
Scheme 98

The aldehyde (252) was prepared by an adaption of the method of Chari and Kozarich.[164] (Scheme 99).

Thus, heating ethyl bromopyruvate with trimethyl orthoformate in refluxing methanol yielded the ester (253) which was converted to the aldehyde (252) by reduction with lithium aluminium hydride and Moffat oxidation of the intermediate carbinol (254).The overall yield for this three step procedure was 32%.


BnO
CO2Et
CN
N
H
+
O
Pr
Br
N
NBn2
(235)
(249)
CN
BnO
CO2Et
N
H
O
NPr
NBn2
7 Steps
BnO
N
N
H
NPr
NBn2
(250)
[H]
HO
N
N
H
NPr
NH2
OHC(CH2)4CHO
HO
N
N
H
NPr
NH
2

Scheme 97

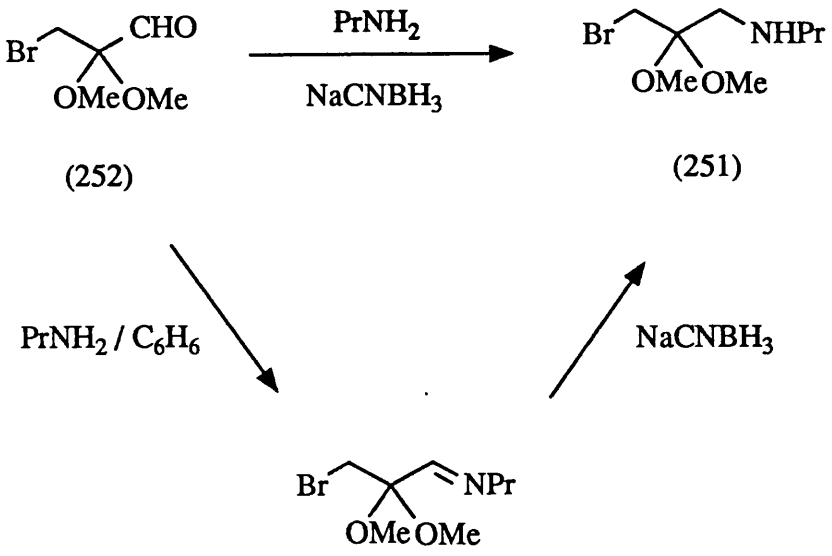


(222) (253)

(254) (252)

Scheme 99

When the aldehyde (252) was heated with n-propylamine in refluxing benzene, the imine (255) was obtained and reduction ($NaCNBH_3$/methanol/acetic acid) of this compound then afforded the amine (251) in 60% overall yield for the two steps. (Scheme 100).



(252) (251)

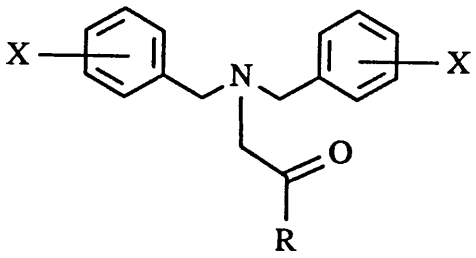
(255)

Scheme 100

In an alternative preparation, the aldehyde (252) and n-propylamine were stirred with sodium cyanoborohydride in acetic acid and methanol (1 : 10) at ambient temperature for 7 hours to produce the required amine (251) directly in 62% yield.

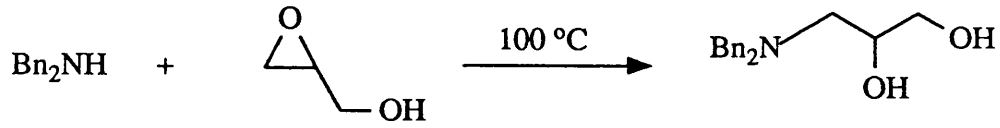
(Scheme 100).

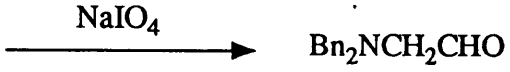
The synthesis of the amino aldehyde (250) was addressed next. A search of the literature revealed that dibenzylamines of the type (256) had been synthesised,[165,168] where R is either alkyl or aryl.



(256)

Using an adaption of the procedure employed by Sainsbury *et al.*,[168] the aldehyde (250) was prepared by a two step procedure. (Scheme 101).



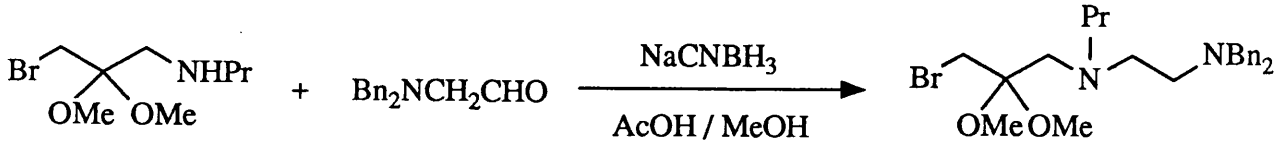


(250)

Scheme 101

Thus, a mixture of dibenzylamine and glycidol was heated at 100°C for three hours. The mixture was then allowed to cool before chloroform and an aqueous solution of sodium metaperiodate were added. The pH of the aqueous phase was adjusted to approximately eight and the two phase system vigorously stirred for three hours. Finally, the chloroform layer was separated and evaporated, at reduced pressure, to yield the required aldehyde (250), as a light orange oil. This compound

proved to be unstable and was used immediately in subsequent work. Hence, a mixture of the acetal (251) and the aldehyde (250) was stirred with sodium cyanoborohydride in acetic acid and methanol for five days. After work up, the desired amine (257) was obtained, as a near colourless solid, in 65% yield. (Scheme 102).



(251) (250) (257)

Scheme 102

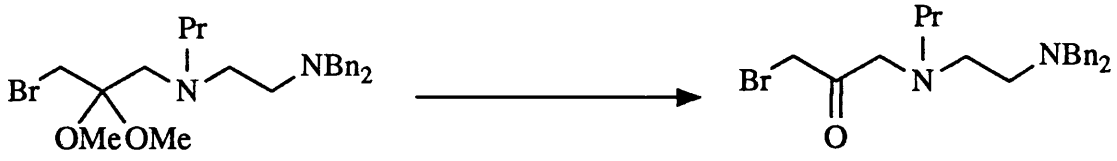
Hydrolysis of the acetal (257) to the ketone (249) was now required before alkylation of the indole (235).

Acetals are generally converted to their corresponding aldehydes or ketones by mild acidic hydrolysis or transacetalisation.[166] Acids typically used for this transformation are hydrochloric,[167] sulphuric,[171] trifluoroacetic acid[167] and pyridinium tosylate.[174] Deacetalisations have also been undertaken in acidic media using solid catalysts such as wet silica gel[172] or Amberlyst 15 resin.[173] Non-aqueous deacetalisations have been achieved by using trimethylsilyl iodide,[175] boron tribromide[176] and titanium tetrachloride.[177]

However, treatment of our acetal (257) with various acids to effect hydrolysis or transacetalisation produced no reaction. Treatment of the acetal (257) with Lewis acids in non-aqueous media did not produce the desired ketone (249) either. (These experiments are summarised in Table 5).

The only experiment which produced a new, identifiable product was that in which the acetal was treated with one molecular equivalent of trimethylsilyl iodide in

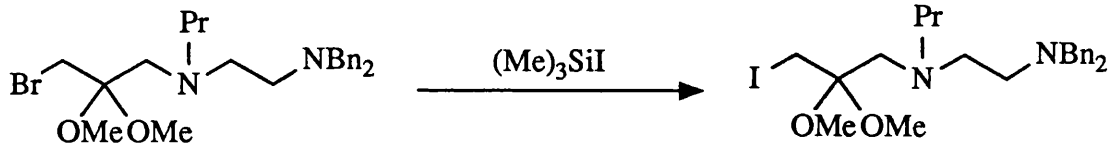
Table Five



(257) (249)

Reagent	Conditions	Result
50% Aqueous CF_3CO_2H	$CHCl_3$ / 5h	No Reaction
98% HCO_2H	85 °C / 3days	No Reaction
$(CH_3)_3SiI$ (1·1 Equivs)	90 min	(258),95%
$(CH_3)_3SiI$ (2·2 Equivs)	21h	(258),99%
SiO_2 / 2N H_2SO_4	2 days	No Reaction
Amberlyst 15 Resin	Acetone / 5 days	No Reaction
2N HCl	80 °C / 6h	No Reaction
$BF_3{\cdot}OEt_2$ / NaBr	CH_2Cl_2 / 3 days	No Reaction
$TiCl_4$	CH_2Cl_2 / 2 days	No Reaction
BBr_3	CH_2Cl_2 / 24h	Complex Product

dry DCM. T.l.c. analysis of the reaction indicated total consumption of the starting acetal, within ten minutes, and the appearance of a less polar product. The crude product, after work up, gave a colourless foam. ^1H n.m.r. spectral analysis of this material showed it to be almost identical to the starting material (257). Thus, the spectrum contained two singlet resonances at 3.17 and 3.14 ppm, corresponding to the two sets of acetal methoxy protons.A mass spectrum of the product,however, indicated that halide exchange had occurred. (Scheme 103).



(257) (258)

Scheme 103

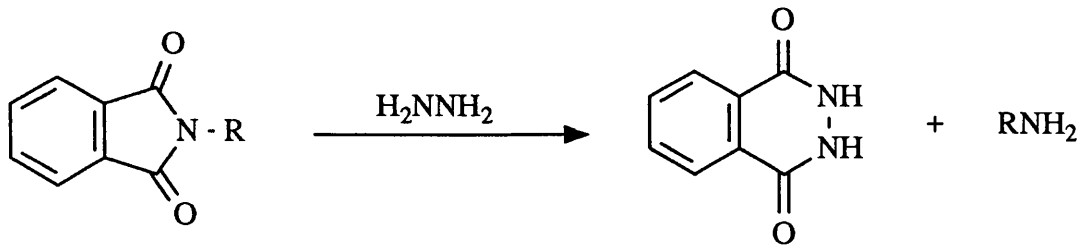
Repitition of the experiment, now with 2.2 molecular equivalents of trimethylsilyl iodide, gave a similar result.

These results were extremely disappointing and it was decided to develop a new approach.

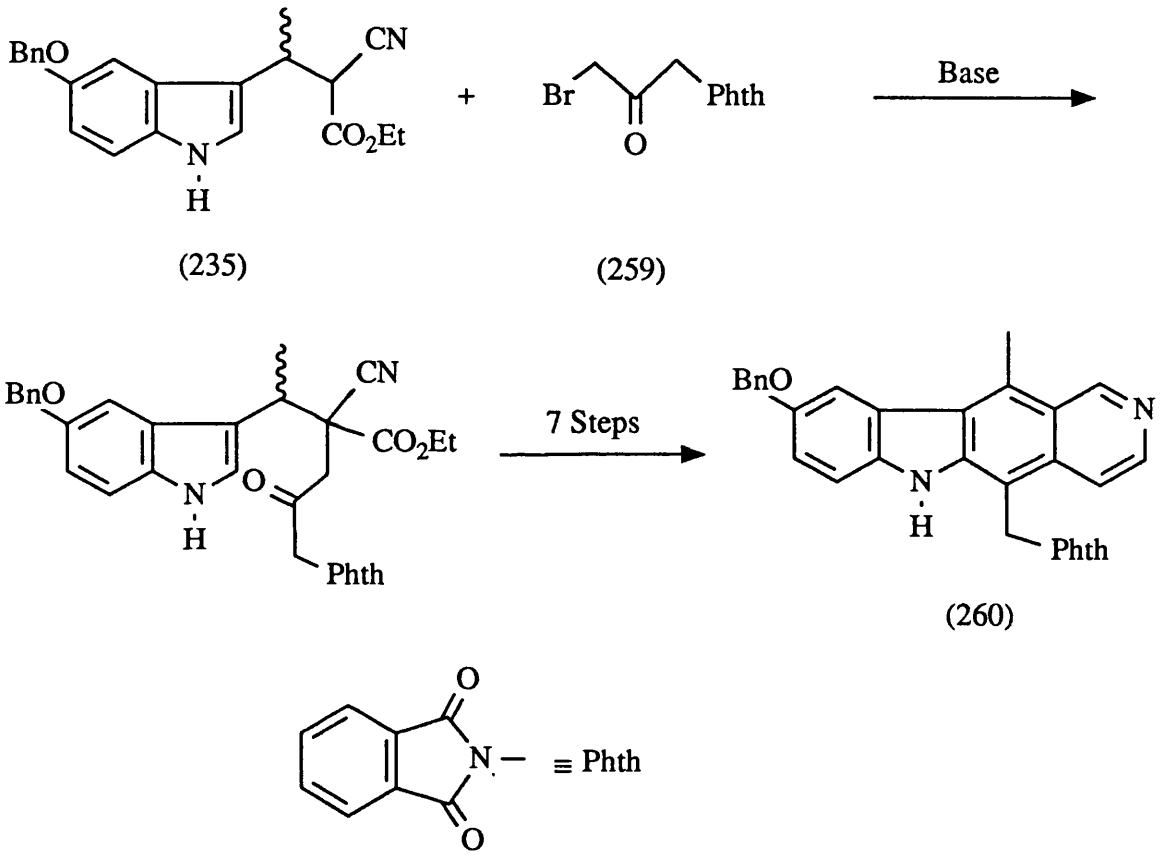
As an amino group in the side chain was desirable, we considered using the phthalimide group as a protected primary amine.

Hydrolysis of phthalimides, using either acid or base catalysis, regenerates corresponding primary amines. Acid catalysis can be used but this is usually a very slow reaction. Better methods include the Ing-Manske procedure,[178] in which the phthalimide is heated with hydrazine in an exchange reaction. (Scheme 104).

Hence, we chose to synthesise the bromo ketone (259) [(247), R = phthalimidyl], with a view to its elaboration to the ellipticine (260). (Scheme 105).



Scheme 104

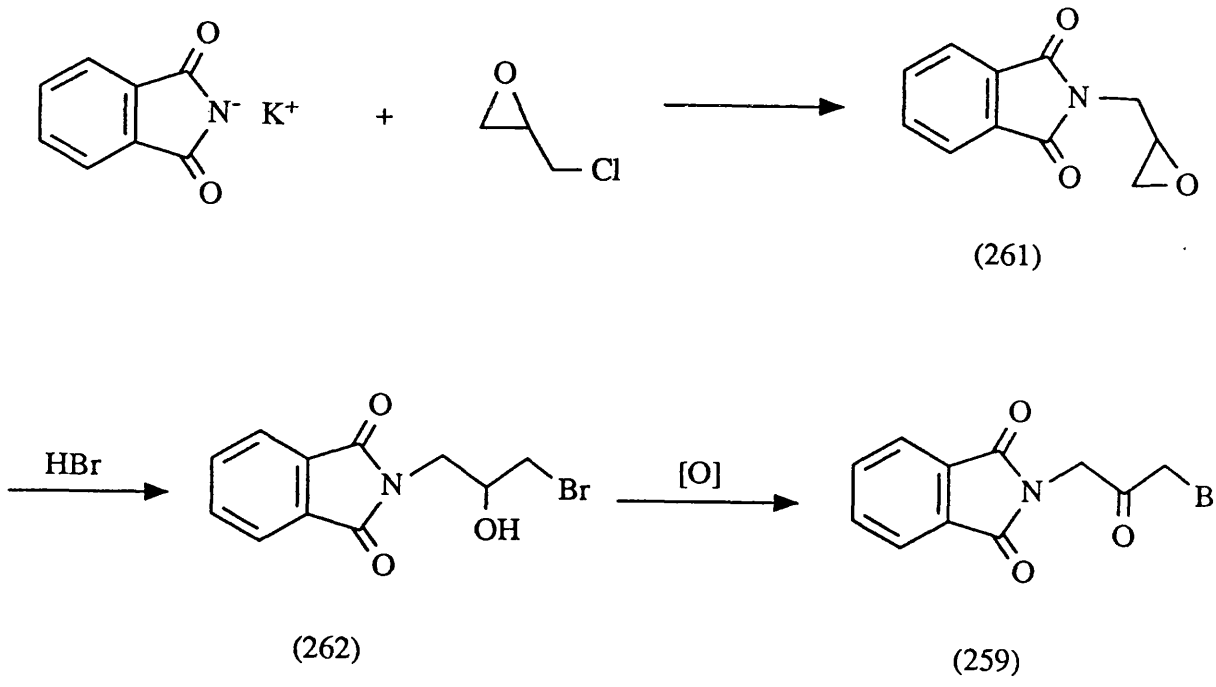


Scheme 105

A search of the literature revealed that the bromo ketone (259) had already been reported.[179] (Scheme 106).

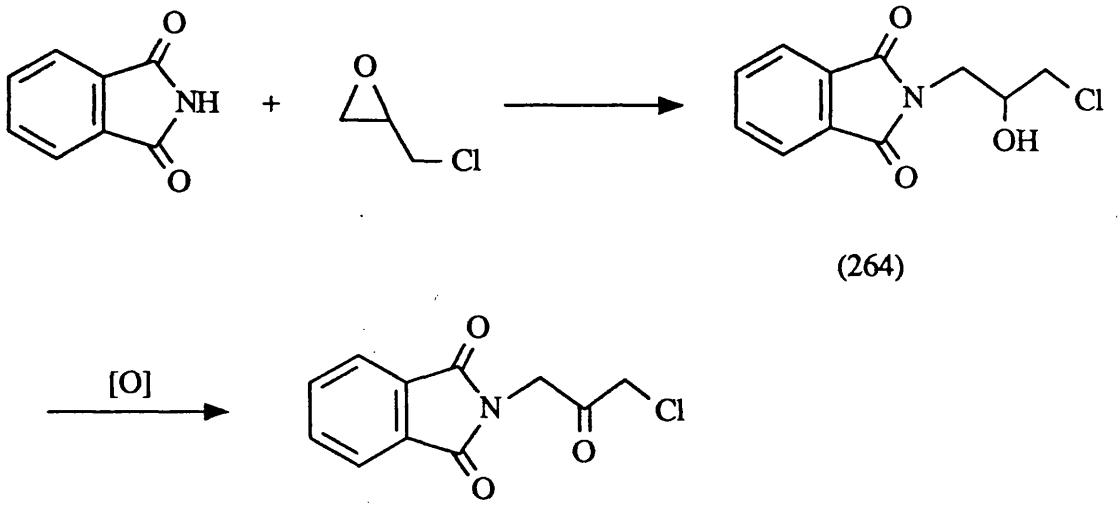
Thus, reaction of potassium phthalimide with epichlorohydrin in DMF produces the epoxide (261) in 52% yield. In our hands, when a solution of the epoxide (261) in

DCM was treated with hydrogen bromide, a quantitative yield of the bromo compound (262) was obtained. Jones oxidation of this compound (262) gave the required bromo ketone (259) in 72% yield.



Scheme 106

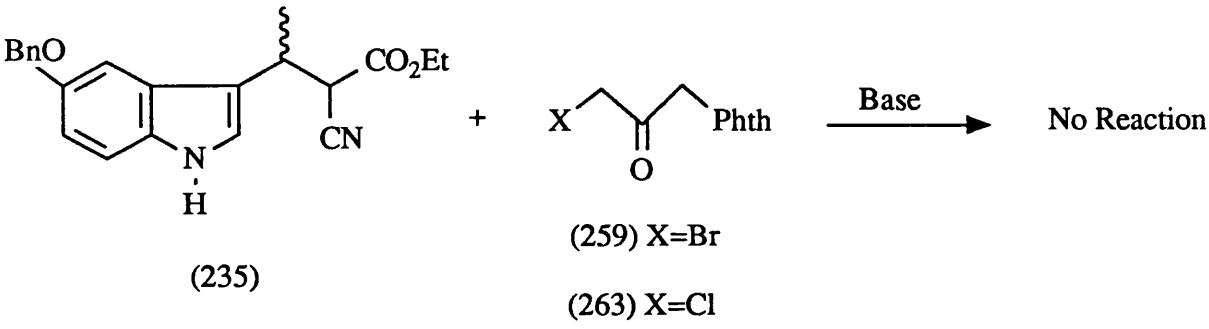
An alternative procedure was employed for large scale preparation of the chloro ketone (263). (Scheme 107).



Scheme 107

Heating phthalimide in epichlorohydrin produced the chloro compound (264).[180] Jones oxidation of this product gave a 72% yield of the required chloro ketone (263).

Alkylation of the indole (235) with haloketones (263) and (259) was then attempted. Disappointingly, this reaction was unsuccessful. Various methods were tried, such as heating the reactants in DMF, but only the starting indole was returned.(Scheme 108).



Scheme 108

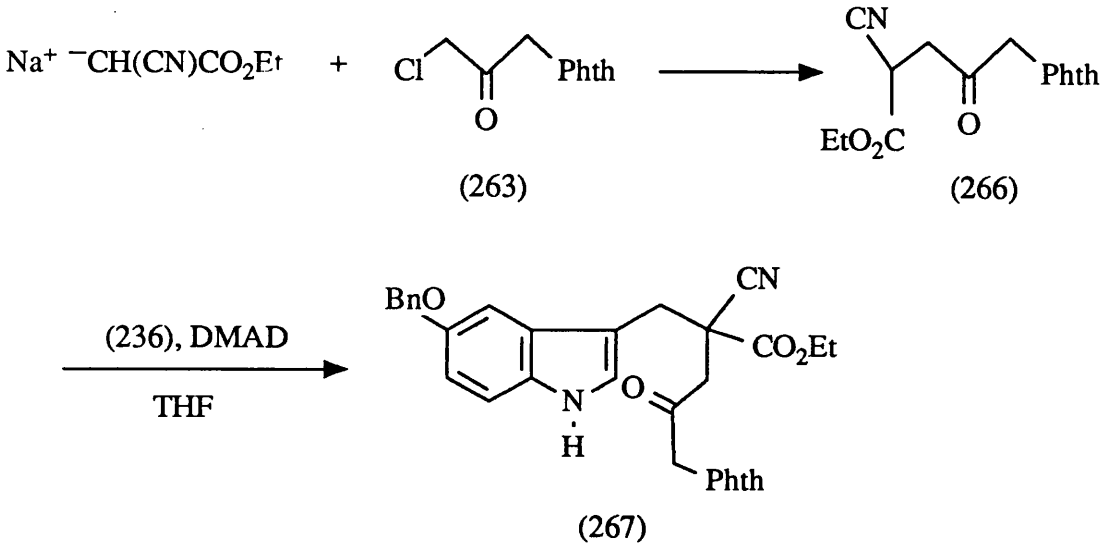
The reaction was then attempted in boiling DMF, in the presence of Na_2CO_3, to try and force the reaction to proceed. Monitoring the reaction by t.l.c. indicated total consumption of starting material after two hours and the formation of a less polar product.

This product was isolated and characterised as 5-benzyloxyindole (265), indicating that under the high temperatures employed, the indole compound (235) had degraded.

The reason for this unsuccessful alkylation was presumed to be due to steric hindrance since the indole (235) had reacted successfully with other alkylating agents

such as chloroacetone and ethyl 3-bromo-2-methoxyiminopropanoate (229). The phthalimidyl bromo ketone (259), however, is much bulkier and it seems probable that its approach to the indole is impaired.

This setback was solved by reverting to our original strategy. (Scheme 109).



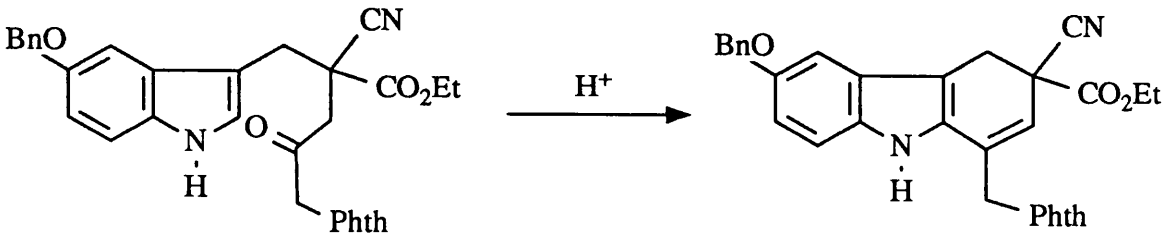
Scheme 109

Hence, the anion of ethyl cyanoacetate was alkylated by the chloro ketone (263) in dry DMF to produce the ketone (266) as a colourless solid in 82% yield.

Reaction of the ketone (266) with the gramine (236) in the presence of DMAD produced the indole (267), as a pale yellow solid, in 80% yield.

We were now in a position to attempt the acid catalysed ring closure of the indole (267) to the dihydrocarbazole (268). (Scheme 110).

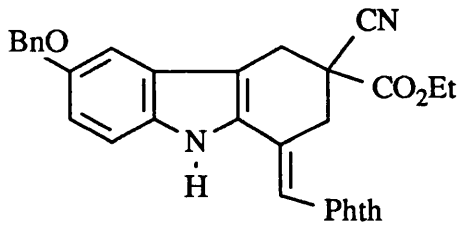
We were curious to see whether this ring closure would occur smoothly, in contrast to the ring closure of the indole (234) to the dihydrocarbazole (241). (Scheme 92).



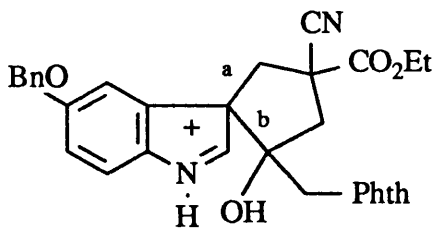
(267) (268)

Scheme 110

Initial conditions employed gave slightly disappointing results but when the indole (267) was heated with *p*-toluene sulphonic acid in boiling toluene, a mixture of the two isomers (268) and (269) were isolated in 96% yield. (These reactions are summarised in Table 6). The nature of these isomers was confirmed by ^{1}H n.m.r. spectral analysis, but when the mixture was allowed to crystallise from ethyl acetate/pet.ether, a pale yellow solid was obtained which proved to be exclusively the exocyclic double bond compound (269), in 18% yield. The mother liquor contained a mixture of the isomers (268) and (269), but no more product could be crystallised.



(269)

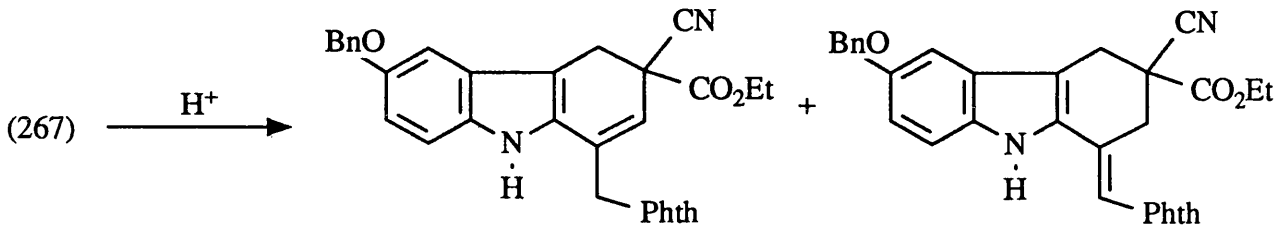


(270)

This efficient cyclisation of the indole (267) is in direct contrast to that observed with the indole (234). One reason for this smooth reaction could be due to the lack of an electron withdrawing function in the spirocyclic intermediate (270), allowing the migration of bond (b), to occur more readily. (See earlier discussion).

With this result in hand, it was attempted to de-ethoxycarbonylate the product

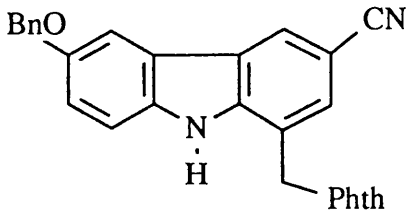
Table Six



(268) (269)

Reagent	Conditions	Yield
Polyphosphate Ester	$CHCl_3$ / Reflux / 11h	41%
50% Aqueous AcOH	Reflux / 9h	25%
50% Aqueous AcOH	THF / Reflux / 9h	35%
p-TsOH	Toluene / Reflux / 30 min	96%

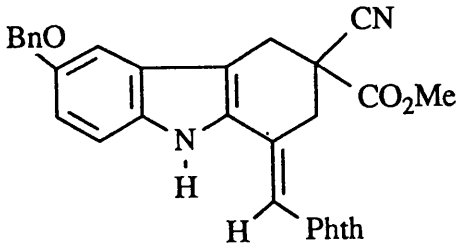
(269) and oxidise it to the carbazole (271).



(271)

Unfortunately, when a mixture of carbazoles (268) and (269) was heated in DMSO containing lithium chloride, no reaction occurred and led only to a poor recovery of starting material. We thought that perhaps it would need less stringent conditions to demethoxycarbonylate our compound rather than to effect a de-ethoxycarbonylation.

Hence, we attempted to transesterify the ethyl ester (269) and obtain the methyl ester (272), by stirring it in a large volume of methanol with a catalytic amount of p-toluene sulphonic acid.

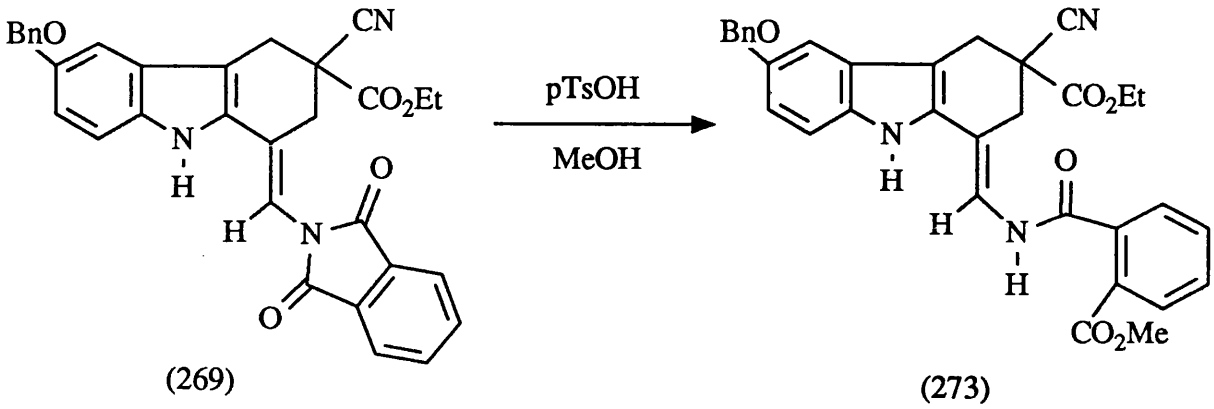


(272)

After twenty-four hours reaction time, the solvent was removed and a more polar product was isolated by column chromatography. However, the product was not the expected methyl ester (272), but rather the amide (273). (Scheme 111).

A trace of the methyl ester (5%) could be detected by ^{1}H n.m.r. analysis, but the

amide (273) was obtained as a yellow solid in 93% yield (based on recovered starting material).



(269) (273)

Scheme 111

To authenticate the structure of the product as that of the tetrahydrocarbazole (273), a nuclear Overhauser enhancement (n.O.e.) experiment was undertaken. When the amide (N-H) doublet at 10.33 ppm was irradiated, an enhancement at 7.72 ppm, corresponding to the resonance of the olefinic proton, was observed.

A decoupling experiment was also carried out. Thus, when the amide (N-H) doublet at 10.33 ppm was irradiated, the doublet at 7.72 ppm collapsed to a singlet, thus confirming the assigned structure.

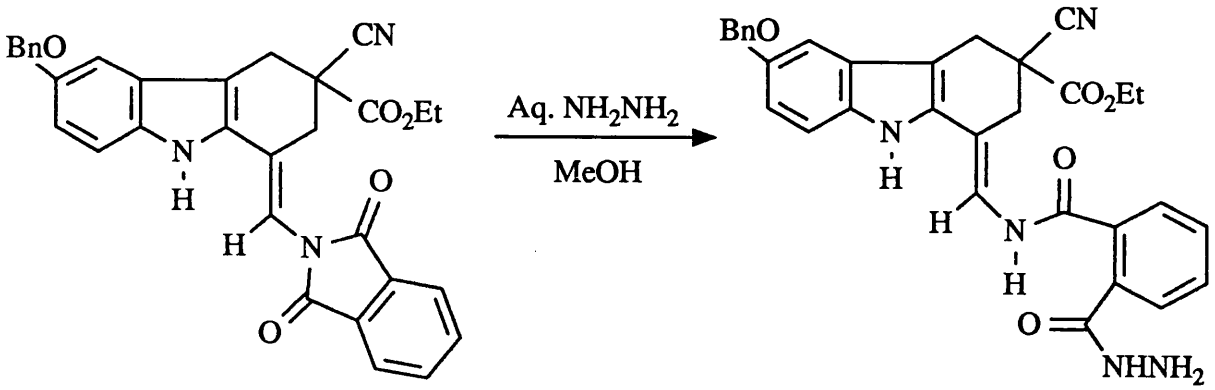
The formation of this product (273) can be explained by nucleophilic attack, and subsequent ring opening of the phthalimide, by methanol.

This type of nucleophilic attack on the carbonyl functions of phthalimides is utilised in the hydrolysis of such compounds to amines.

In our hands, reaction of the tetrahydrocarbazole (269) with hydrazine gave the corresponding product (274) in 41% yield. (Scheme 112).

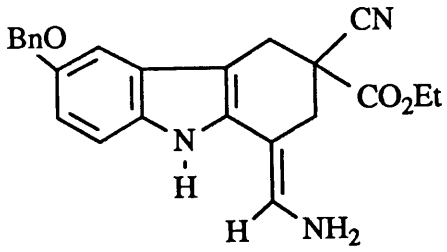
Disappointingly, attempts to transform the product (274) into the free amine

(275) were unsuccessful.



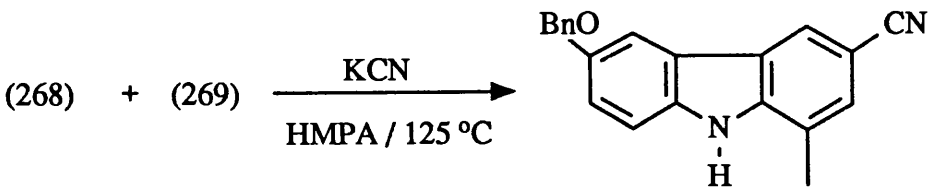
(269) (274)

Scheme 112



(275)

While these experiments were undertaken, efforts were still being made to de-ethoxycarbonylate the carbazoles (268) and (269). Thus. heating the mixture of the compounds (268) and (269) with potassium cyanide in hexamethylphosphoramide (HMPA) at 125°C for 48h led to the isolation of 6-benzyloxy-3-cyano-1-methylcarbazole (276). (Scheme 113).

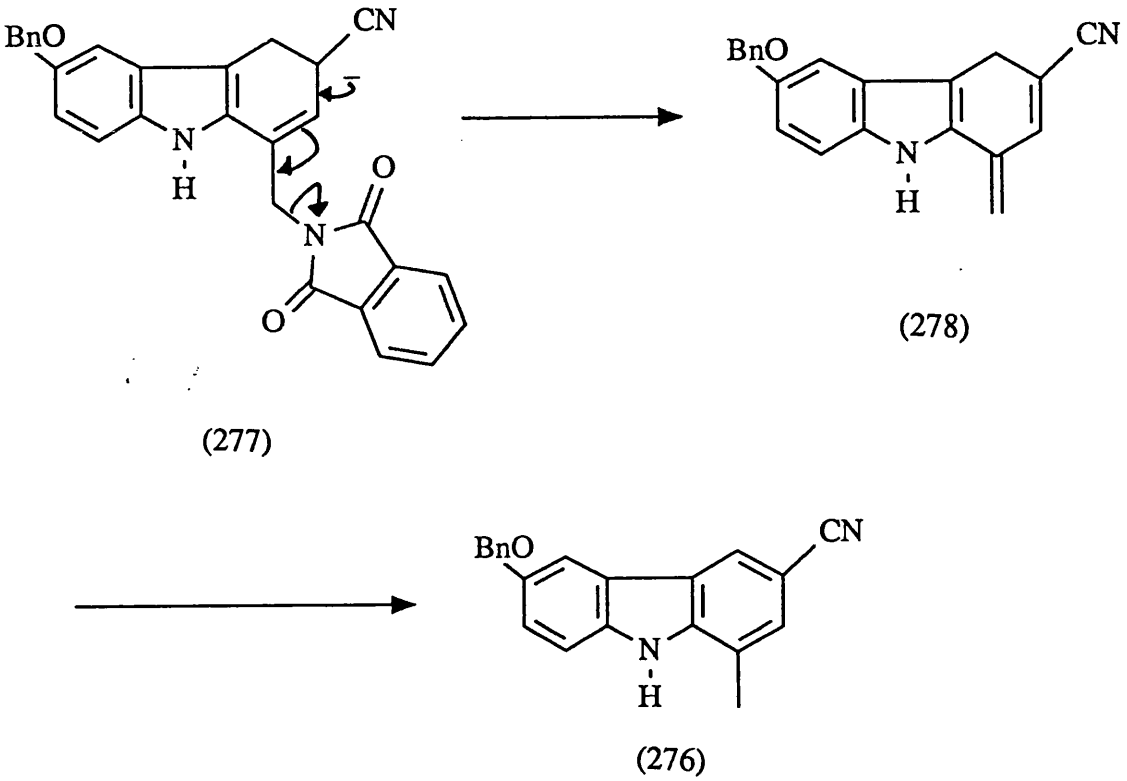


(276)

Scheme 113

This transformation can be envisaged as proceeding *via* the required

de-ethoxycarbonylation, but the intermediate anion (277) now eliminates phthalimide anion to afford the diene (278). This compound undergoes a 1,5-hydrogen shift to yield the fully aromatised carbazole (276). (Scheme 114) [See also Scheme 59].

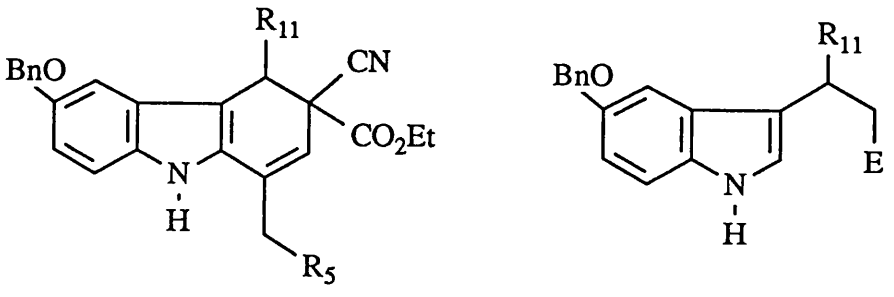


(277) (278) (276)

Scheme 114

Although this result was disappointing, it has illustrated another limitation of our methodology.

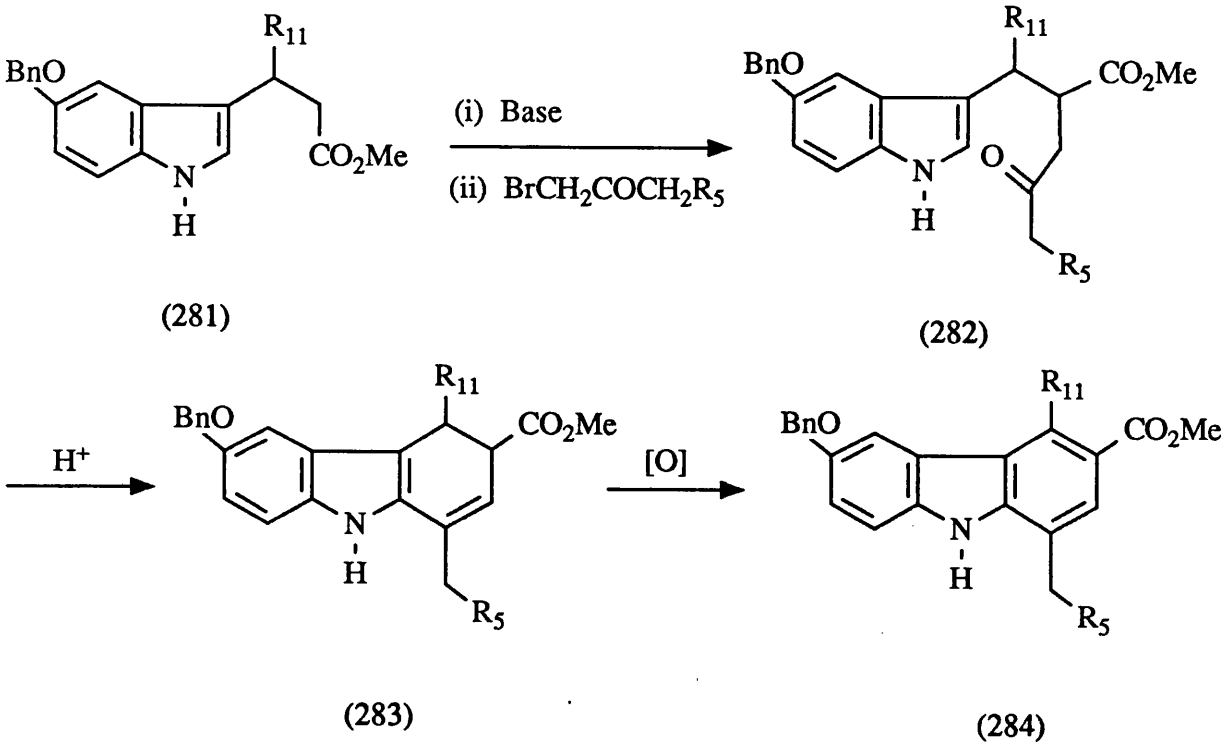
Thus, intermediates of the type (279), where R_5 can act as a leaving group must be avoided.



(279) (280)

A possible way of surmounting this problem would be to alkylate intermediates of the type (280), where E represents an electron withdrawing group such as a nitrile or an alkoxycarbonyl unit.

This would then prevent the dealkoxycarbonylation step and leave only an oxidation of the dihydrocarbazole (283) to afford the corresponding carbazole (284). (Scheme 115).

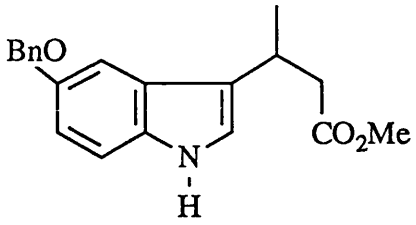


Scheme 115

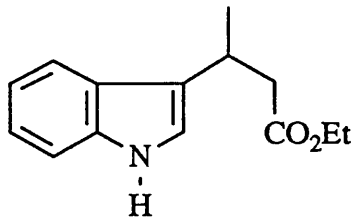
There is literature precedent for this type of alkylation of nitriles[181] and esters.[182] As only one activating group is present, a strong base such as lithium diisopropylamide (LDA) is preferred, but phase transfer catalysis or heating with weaker bases have also been employed.

Methyl 3-(5-benzyloxy-3-indolyl)butanoate (285) and ethyl

3-(3-indolyl)butanoate (286) were synthesised according to the method of Oikama *et al.*[183]



(285)

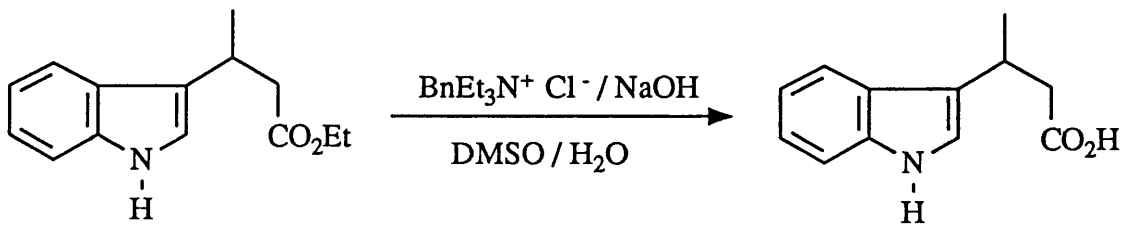


(286)

In the limited time left at the end of this project, the author attempted to alkylate these compounds. However, successful conditions were not found.

For example, due to the acidic nature of the indole N-H, two equivalents of base and alkylating agent were employed. (These results are summarised in Table Seven). In most cases, the starting materials were returned unchanged, but when higher temperatures were employed, the alkylating agent was destroyed.

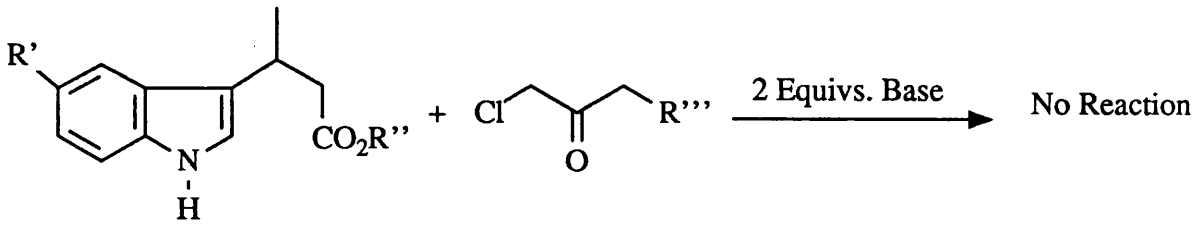
Recourse to phase transfer conditions were equally unsuccessful, and under the conditions employed, the ester (286) was saponified to the free acid (287). (Scheme 116).



(286) (287)

Scheme 116

Table Seven



R'	R''	R'''	Base	Conditions
$PhCH_2O$	CH_3	H	Na_2CO_3	DMF / 1h
$PhCH_2O$	CH_3	H	Na_2CO_3	DMF / 100 °C / 1h
H	C_2H_5	H	NaH	THF / 24h
H	C_2H_5	H	NaH	THF / 70 °C / 7h
H	C_2H_5	H	LDA	THF / - 78 → 25 °C / 24h
H	C_2H_5	H	NaH	DMF / 110 °C / 14h
H	C_2H_5	Phth	NaH	DMF / 100 °C / 10h

There are obviously several experiments outstanding and one could, for example, protect the indolic nitrogen of (285) by sulphonylation.

It is expected that the challenge presented by these results will be taken up by future workers joining our group at Bath, as there is continuing international interest in the target alkylaminoellipticines.

EXPERIMENTAL

General

Melting points were recorded on an Electrothermal Mark II apparatus and are uncorrected. I.r. spectra were recorded on Perkin-Elmer 197 or 1310 grating spectrophotometers. U.v. spectra were recorded on Perkin-Elmer 402 and Lambda 3 instruments. ^{1}H N.m.r. spectra were run at 60 MHz on Perkin-Elmer R24B and Varian EM360 spectrometers; at 250 MHz on a Bruker instrument using the facility at Glaxo Group Research, Greenford; at 270 MHz on a JEOL JNM Fourier Transform spectrometer. ^{13}C N.m.r. were recorded at 67.8 MHz on a JEOL JNM Fourier Transform spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) as internal standard. Mass spectra and high resolution accurate mass measurements were determined on a VG 7070E instrument with VG 2000 data system. T.l.c. analysis was performed on Merck DC-Alufolien plates coated with Kieselgel 60 F_{254}. Visualisation of reaction components was by u.v. light. Column chromatography was performed in short path columns packed with Merck 7736 Kieselgel and the solvent was eluted under pressure provided by hand bellows. Dry column chromatography was performed in cylindrical sinters packed with Merck 7736 Kieselgel and the solvent was eluted under water pump vacuum. Evaporations were carried out under water pump vacuum unless otherwise stated. Ethyl acetate, dichloromethane and pet. ether used for chromatography were distilled prior to use. The term pet. ether refers to light petroleum ether boiling at 60-80°C.

Reagents

Tetrahydrofuran was dried by distillation from sodium/benzophenone ketyl. Diethyl ether and benzene were dried by standing over sodium wire for at least 1 day. Dichloromethane was dried by distillation from calcium hydride. Dimethyl sulphoxide

was dried by standing over activated 4 A° molecular sieves. Methanol and ethanol were dried by distillation from magnesium turnings. Triethylamine was dried by distillation from calcium hydride. Dimethylformamide was dried by standing over activated 4 A° molecular sieves. Tosyl chloride was recrystallised from pet. ether prior to use. All molecular sieves were activated by heating to at least 150°C overnight. Unless otherwise stated, all other solvents and reagents were used as supplied.

Experimental

2-Cyano-4-oxopentanonitrile (165a)

A solution of malononitrile (3.3g, 50 mmol) in dry THF (10 cm^3) was added, dropwise, to a cooled, stirred suspension of sodium hydride (1.2g, 50 mmol) in dry THF (30 cm^3) under a nitrogen atmosphere.

After the addition, the ice bath was removed and the reaction mixture stirred for a further 30 minutes before the resultant suspension was slowly injected, *via* a cannula, into a cooled solution of chloroacetone (5.3 cm^3, 66 mmol) in dry THF (30 cm^3).

The reaction mixture was stirred for 1h before the solvent was removed at reduced pressure. The residue was purified by bulb to bulb distillation (220°C/0.3 mmHg) to yield 4.9g (79%) of colourless crystals which were recrystallised from chloroform/pet. ether; m.p. = 55-56°C, (lit[134] 55-57°C); ν_{max} ($CHCl_3$)cm^{-1}2200 (C≡N), 1700 (C=O); δ_H ($CDCl_3$) ppm 4.21 (1H, t, J = 6Hz, C<u>H</u>), 3.25 (2H, d, J= 6Hz, C<u>H</u>$_2$), 2.30 (3H, s, C<u>H</u>$_3$); m/z (70eV) 43 (100%), (C.I.), 123 [$(M+1)^+$, 100%].

Ethyl 2-cyano-4-oxopentanoate (165b)

Sodium metal (5g, 0.22 mol) was completely dissolved in absolute ethanol (100 cm^3), with cooling. To this solution was added ethyl cyanoacetate (25 cm^3, 0.22 mol) with the temperature maintained below 20°C.

After the addition, stirring was continued at room temperature for a further 30 minutes. The resultant suspension was then slowly transferred, *via* a cannula, into a stirred solution of chloroacetone (20 cm^3, 0.25 cm^3), again keeping the temperature below 20°C.

The reaction mixture was stirred for 1h before the solvent was removed at reduced pressure and the residue partitioned between ethyl acetate (100 cm^3) and water (100 cm^3)

The organic extract was washed with water (2 x 100 cm^3), dried ($MgSO_4$) and

evaporated at reduced pressure.

The residue was purified by bulb to bulb distillation (95°C/0.5 mmHg; lit[186] 69-72°C/0.01 mmHg) to yield the title compound as a colourless oil (24g, 64%). ν_{max} (thin film) cm^{-1} 2260 (C≡N), 1745 (C=O), 1725 (C=O); δ_H ($CDCl_3$) ppm 4.17 (2H, q, *J* = 6Hz, $OC\underline{H}_2$), 3.82 (1H, t, *J* = 6Hz, C<u>H</u>), 3.05 (2H, d, *J* = 6Hz, $CHC\underline{H}_2$), 2.18 (3H, s, $C\underline{H}_3C$=O), 1.28 (3H, t, *J* = 6Hz, $OCH_2C\underline{H}_3$); m/z (low eV) 169 (M^+, 16%), 43 (100%)

*Ethyl 2-Acetyl-4-oxopentanoate (*165c*)*

Sodium metal (5g, 0.22 mol) was completely dissolved in absolute ethanol (100 cm^3), with cooling. To this solution was added, dropwise, ethyl acetoacetate (27.8 cm^3, 0.22 mol) with the temperature maintained below 20°C.

After the addition, stirring was continued at room temperature for a further 30 minutes. The resultant white suspension was then slowly transferred, *via* a cannula, into a stirred solution of chloroacetone (20 cm^3, 0.25 mol) in absolute ethanol (100 cm^3), again keeping the temperature below 20°C.

The reaction mixture was stirred for 30 minutes before the solvent was removed at reduced pressure and the residue partitioned betwen ethyl acetate (100 cm^3) and water (100 cm^3).

The organic extract was washed with water (2 x 100 cm^3), dried ($MgSO_4$) and the solvent removed.

The residue was purified by bulb to bulb distillation (80-81°C/0.2 mmHg, lit[135] 126-128°C/14 mmHg) to yield the title compound as a colourless oil (26.7g, 66%), ν_{max} (thin film) cm^{-1} 1688 (C=O), 1713 (C=O); δ_H ($CDCl_3$)ppm 4.18 (2H, q, *J* = 7Hz, $OC\underline{H}_2$), 3.82 (1H, t, *J* = 6Hz, C<u>H</u>), 3.05 (2H, d, *J* = 6Hz, $CHC\underline{H}_2$), 2.34 (3H, s, $C\underline{H}_3C$=O), 2.19 (3H, s, $C\underline{H}_3C$=O), 1.29 (3H, t, *J* = 7Hz, $OCH_2C\underline{H}_3$); m/z (70 eV) 101 (28%), 43 (100%), (C.I.) 187 [$(M+1)^+$, 93%], 169 (58%), 141 (100%), 131 (22%); $C_9H_{14}O_4$: Requires C 58.1, H 7.5%; Found C 58.2, H 7.8%.

4,4-*Dicyano*-5-(3-*indolyl*)*pentan*-2-*one* (167a)

A solution of the ketone (165a) (2g, 16.4 mmol) and dimethyl acetylenedicarboxylate (2.01 cm^3, 16.4 mmol) in dry THF (15 cm^3) was added, dropwise, to a cooled solution of gramine (2.85g, 16.4 mmol) in dry THF (40 cm^3), under a nitrogen atmosphere.

The reaction mixture was stirred for 3h. The solvent was removed at reduced pressure and the residue purified by column chromatography (pet. ether: ethyl acetate/ 50:50, $R_f = 0.65$). The title compound was isolated as white plates (2.90g, 71%), recrystallised from ethyl acetate/pet. ether, m.p. = 125-126°C, ν_{max} ($CHCl_3$) cm^{-1} 3410 (N-H), 2200 (C≡N), 1680 (C=O); δ_H ($d_6$acetone) ppm 10.40 (1H, s, exchanges, N-H), 7.70 - 6.90 (5H, m, aromatic protons), 3.52 + 3.35 (2 x 2H, 2 x s, 2 x CH_2), 2.10 (3H, s, CH_3); m/z (low eV) 251 (M^+, 75%), 130 (100%), (70eV) 251 (M^+, 10%), 130 (100%); λ_{max} (95% Ethanol) nm 289, 280, 219; $C_{15}H_{13}N_3O$: Requires C 71.7, H 5.2, N 16.7%; Found C, 71.7; H, 5.2; N, 16.5%; Acc. Mass; Calculated 251.1057; Found 251.0998.

4-*Cyano*-4-*ethoxycarbonyl*-5-(3-*indolyl*)*pentan*-2-*one* (167b)

The same procedure used for the synthesis of the indole (167a), converted the ketone (165b) (1.5g, 8.88 mmol) to the indole (167b) (2.60g, 98%). The title compound was isolated as colourless crystals, recrystallised from ethyl acetate/pet. ether, m.p. = 148°C, (lit[134] 145-146°C); $R_f = 0.9$ (pet. ether : ethyl acetate : triethylamine/80 : 20 : 20), ν_{max} (nujol) cm^{-1} 3420 (N-H), 2250 (C≡N), 1730 (C=O), 1710 (C=O); δ_H (d^6 acetone) ppm 10.50 (1H, s, exchanges, N-H), 7.50-6.70 (5H, m, aromatic protons), 3.92 (2H, q, J = 6Hz, OCH_2CH_3), 3.40-3.20 (4H, m, 2 x CH_2), 2.07 (3H, s, CH_3 C=O), 1.12 (3H, t, J = 6Hz, OCH_2CH_3); λ_{max} (95% Ethanol) nm (ϵ)289 (2600), 281 (3000), 221 (1400); m/z (low eV) 298 (M^+, 61%), 130 (100%), (70eV) 298 (M^+, 10%), 130 (100%), 43 (23%), $C_{17}H_{18}N_2O_3$: Requires C, 68.5; H, 6.0; N, 9.4%; Found C, 68.1; H, 6.2; N 9.4%.

4-*Acetyl*-4-*ethoxycarbonyl*-5-(3-*indolyl*)*pentan*-2-*one* (167c)

Method A

To a stirred solution of gramine (4.35g, 25 mmol) in dry THF (30 cm^3), under a nitrogen atmosphere, was slowly added a solution of freshly distilled dimethyl sulphate (2.4 cm^3, 3.14g, 25 mmol) in dry THF (25 cm^3). On addition, a pink gum was observed.

In a separate flask, a solution of the ketone (165c) (4.23g, 25 mmol) in dry THF (35 cm^3) was slowly added to a stirred cooled suspension of NaH (0.6g, 25 mmol) in dry THF (15 cm^3).

After the addition was complete, the ice bath was removed and the mixture stirred at ambient temperature for 30 minutes. The resultant purple anion solution was then slowly transferred, *via* a cannula, into the methiosulphate reaction vessel. The mixture was shaken until stirring was possible.

The mixture was stirred for 16h before the solvent was removed and the residue partioned between chloroform (25 cm^3) and 2N HCl (25 cm^3). The aqueous layer was washed with chloroform (2 x 15 cm^3) and the combined organic layers were washed with water (2 x 25 cm^3), brine (25 cm^3) and dried ($MgSO_4$).

The solvent was removed at reduced pressure and the residue purified by column chromatography (pet. ether/ethyl acetate) to yield the title compound as a pale red oil (6.22g, 79%).

All attempts to crystallise this product failed. The product was used without further purification after column chromatography. $R_f = 0.61$ (pet. ether : ethyl acetate/80:20). ν_{max} ($CHCl_3$) cm^{-1} 3400 (N-H), 1710 (C=O), 1750 (C=O); δ_H ($CDCl_3$) ppm 8.83 (1H, s, exchanges, N-H), 7.40-6.78 (5H, m, aromatic protons), 4.13 (2H, q, J = 7Hz, OCH_2CH_3), 3.50 (2H, q, J = 4Hz, CH_2), 3.05 (2H, s, CH_2), 2.38 + 1.92 (2 x 3H, 2 x s, 2 x CH_3C=O), 1.16 (2H, t, J = 7Hz, OCH_2CH_3); δ_C ($CDCl_3$) ppm 206.9 (C=O), 205.8 (C=O), 171.4 (CO_2Et), 135.6 (indole C-8), 127.7 (indole C-9), 123.1 (indole C-2), 121.6, 119, 117, 111 (indole C-4, C-5, C-6, C-7), 108 (indole C-3), 62.6 [C ($COCH_3$) CO_2Et] 61.3 (CH_2), 46.4 (CH_2COCH_3), 29.5 (CH_3 C=O), 28.8 (OCH_2CH_3), 27.4 ($COCH_3$), 13.5 ($CO_2CH_2CH_3$); m/z (C.I.) 315 (M^+, 32%), 130 (100%).

Method B

The same procedure used for the synthesis of the indole (167a) was employed to convert the ketone (165c) (1.99g, 10.84 mmol) into the indole (167c). However, after the work-up procedure and column chromatography (pet.ether/ethyl acetate), the product (167c) was found to be contaminated with the by-product dimethyl 2-dimethyl aminobutenedioate (182). Extensive column chromatography could only partially separate the two compounds. Consequently, the method was deemed unsatisfactory and Method A was employed for the synthesis of (167c). The enaminoester (182) was isolated as an off-white solid, m.p. = 83-85°C (lit[185] 83-84.5°C); ν_{max} ($CHCl_3$) cm^{-1} 1735 (C=O), 1675 (C=O); δ_H ($CDCl_3$) ppm 4.6 (1H, s, olefinic proton), 3.9 (3H, s, $CO_2C\underline{H}_3$), 3.6 (3H, s, $CO_2C\underline{H}_3$), 2.9 (6H, s, $N(C\underline{H}_3)_2$); m/z (70 eV) 187 (M^+, 40%), 156 (42%), 155 (43%), 128 (100%), 72 (43%),(C.I.) 188 [$(M+1)^+$, 100%], 187 (M^+, 39%), 156 (77%), 128 (30%).

3,3-Dicyano-1,2,3,4-tetrahydro-1-methylenecarbazole (168a)

A solution of the indole (167a) (1.45g, 5.74 mmol) in 50% aqueous acetic acid (75 cm^3) was heated at reflux for 4h. After cooling, the solvent was removed under reduced pressure and the residue partitioned between saturated $NaHCO_3$ solution (75 cm^3) and ethyl acetate (3 x 50 cm^3). The combined organic layers were washed with water (100 cm^3), brine (50 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the title compound as a colourless solid (1.43g, 99%), recrystallised from ethyl acetate, m.p. = 215°C, (lit[134] 226-228°C). R_f = 0.84 (pet.ether : ethyl acetate/50:50). υ_{max} ($CHCl_3$) cm^{-1} 2400 (N-H), 2210 (C≡N), 1620 (C=C); δ_H (d^6 acetone) ppm 10.50 (1H, s, exchanges, N-H), 7.60-6.92 (4H, m, aromatic protons), 5.66 + 5.20 (2 x 1H, 2 x s, olefinic protons), 3.64 + 3.31 (2 x 2H, 2 x s, 2 x $C\underline{H}_2$); λ_{max} (95% Ethanol) nm 305, 272, 212; m/z (low eV) 233 (M^+, 100%), (70eV) 233 (M^+, 100%), 232 (23%), 155 (57%), 149 (30%), 57 (23%); $C_{15}H_{11}N_3$: Requires C 77.2, H 4.8, N 18.0%; Found C 76.8, H 4.7, N 17.7%.

3-*Cyano*-3-*ethoxycarbonyl*-1,2,3,4-*tetrahydro*-1-*methylenec arbazole* (168b)

The procedure used for the synthesis of the tetrahydrocarbazole (168a) was employed to convert the indole (167b) (2.0g, 6.71 mmol) into (168b) (1.86g, 99%). The title compound was isolated as colourless crystals recrystallised from chloroform/pet.ether, m.p. = 133°C, (lit[134] 133-135°C), R_f = 0.59 (pet. ether : ethyl acetate/50:50), ν_{max} ($CHCl_3$) cm^{-1} 3400 (N-H), 2250 (C≡N), 1720 (C=O), 1630 (C=C); δ_H ($CDCl_3$) ppm 8.32 (1H, br s, exchanges, N-H), 7.50-7.10 (4H, m, aromatic protons), 5.20-4.96 (2 x 1H, 2 x s, olefinic protons), 4.30 (2H, q, J = 7Hz, OCH_2CH_3), 3.56 + 3.38 (2 x 2H, 2 x s, 2 x CH_2), 1.31 (3H, t, J = 7Hz, OCH_2CH_3); m/z (low eV) 280 (M^+, 100%), 207 (28%), (70eV), 280 (M^+, 48%), 207 (100%); $C_{17}H_{16}N_2O_2$: Requires C 72.8, H 5.8, N 10.0%; Found C 72.8, H 5.7, N 9.9%; λ_{max} (95% Ethanol) nm (ϵ) 309 (54 500), 305 (54 900), 252 (21 700).

3-*Acetyl*-3-*ethoxycarbonyl*-3,4-d*ihydro*-1-*methylcarbazole* (193).

The procedure used for the synthesis of the tetrahydrocarbazole (168a) was employed to convert the indole (167c) (2.0g, 6.35 mmol) into a mixture of the dihydrocarbazole (193) and the isomeric tetrahydrocarbazole (168c) (1.36g, overall yield of 72%). The mixture was purified by column chromatography (pet.ether/ethyl acetate) to yield a mixture of (193) and (168c).δ_H($CDCl_3$)ppm; 8.80 (0.5H, s, N-H),8.30 (0.5H, s, N-H), 7.60 -7.00 (4H,m,rest of aromatic protons), 5.88 (0.5H, d , J = 1.5 Hz, endocyclic olefinic proton), 5.23 + 5.03 (2 x 0.5H, 2 x s, 2 x exocyclic olefinic protons), 4.52 - 4.04 (2H, m, 2 x OCH_2CH_3), 3.60 - 3.10 (3H, m, 3 x CH_2), 2.21 (3H, s, 2 x $COCH_3$), 2.05 (1.5H, s, $H_2C=CCH_3$), 1.58 - 1.08 (2 x 1.5H, m, 2 x OCH_2CH_3). The title compound could be obtained as colourless crystals by crystallisation from ethyl acetate/pet.ether, m.p. = 131°C, R_f = 0.74 (pet.ether : ethyl acetate/50:50), ν_{max} ($CHCl_3$) cm^{-1} 3420 (N-H), 1700 (C=O); δ_H($CDCl_3$) ppm 8.10 (1H, s, exchanges, N-H), 7.56-7.08 (4H, m, aromatic protons), 5.88 (1H, d, J = 1.5Hz, olefinic proton), 4.24 (2H, q, J = 7Hz, OCH_2CH_3), 3.50 (2H, d, J = 16Hz, CH_2), 2.21 (3H, s, $COCH_3$), 2.11 (3H, d,

J = 1.5Hz, $CH_2 = CC\underline{H}_3$), 1.23 (3H, t, J = 7Hz, $OCH_2C\underline{H}_3$); m/z (low eV) 297 (M^+, 58%), 254 (100%), 144 (48%), 120 (25%), 101 (73%), (70eV) 181 (28%), 101 (34%), 73 (23%), 43 (100%); $C_{18}H_{19}NO_3$: Requires C 72.7, H 6.4, N 4.7%; Found C 72.4, H 6.4, N 4.6%.

3-*Cyano*-1-*Methylcarbazole* (169a)

The tetrahydrocarbazole (168a) (546 mg, 2.34 mmol) was preabsorbed onto silica gel (5.5g) and heated at 250°C under a stream of nitrogen.

After 1h, the silica was allowed to cool and then washed with ethyl acetate (4 x 50 cm^3). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl acetate). The title compound was isolated as a pale yellow solid (198 mg, 41%), recrystallised from ethyl acetate/pet.ether, m.p. = 193°C (lit[134] 193-194°C); R_f = 0.42 (pet.ether:ethyl acetate/80:20), ν_{max} (nujol) cm^{-1} 3450 (N-H), 2200 (C≡N); δ_H (d^6 acetone) ppm 10.83 (1H, br.s, exchanges, N-$\underline{H}$), 8.04 - 6.82 (6H, m, aromatic protons), 2.50 (3H, s, $C\underline{H}_3$); λ_{max} (95% ethanol) nm (ϵ) 336 (1200), 324 (1600), 310 (1900), 273 (21900), 261 (17100); m/z (low eV) 206 (M^+, 100%), (70 eV) 206 (M^+, 100%), 205 (44%), 179 (62%), 151 (31%); $C_{14}H_{10}N_2$: Requires C, 81.5; H, 4.9; N, 13.6%; Found C, 81.4; H, 4.8; N, 13.6%.

3-*Ethoxycarbonyl*-1-*methylcarbazole* (169b)

The tetrahydrocarbazole (168b) (0.39g, 1.39 mmol) was preabsorbed onto silica gel (4g) and heated at 250°C under a stream of nitrogen for 2h.

The silica gel was then allowed to cool and washed with ethyl acetate (4 x 50 cm^3). The solvent was removed and the residue purified by column chromatography (pet. ether/ethyl acetate). The title compound was isolated as a pale yellow solid (180mg, 50%), recrystallised from chloroform/pet.ether, m.p. = 133-135°C, (lit[189] 151°C) R_f = 0.34 (pet. ether : ethyl acetate 80:20), ν_{max} ($CHCl_3$) ppm 3450 (N-H), 1680 (C=O), 1600 (C=C); δ_H ($CDCl_3$) ppm 8.68 (1H, s, $\underline{H}$-4 of carbazole), 8.30 (1H, s, exchanges, N-$\underline{H}$), 8.12-7.25 (5H, m, rest of the aromatic protons), 4.37 (2H,

q, J = 7Hz, $OC\underline{H}_2CH_3$), 2.57 (3H, s, $C\underline{H}_3$), 1.45 (3H, t, J = 7Hz, $OCH_2C\underline{H}_3$); λ_{max} (95% ethanol) nm 278, 269, 235; m/z (low eV) 253 (M^+, 100%), (70eV) 253 (M^+, 65%), 208 (65%), 180 (29%), 68 (32%), 43 (100%), 28 (50%); $C_{16}H_{15}NO_2$: Requires C, 75.9; H, 5.9; N, 5.5%; Found C, 75.9; H, 6.0; N, 5.6%.

A second product was eluted from the column at R_f = 0.42 (pet. ether : ethyl acetate/80:20) and was characterised as 3-*cyano*-1-*methylcarbazole* (169a) (30mg, 10%).

1-methyl-3-(sulphoxymethyl)acetylcarbazole (202)

A solution of sodium hydride (103 mg, 4.29 mmol) in dry DMSO (3 cm^3) was stirred at 60-70°C, under a nitrogen atmosphere, until the evolution of hydrogen gas had ceased and the solution had become a clear, dark green colour (approx 1h). Dry THF (4 cm^3) was added to the anion solution and the mixture cooled in an ice bath.

A solution of the ester (169b) (363 mg, 1.4 mmol) in dry THF (4 cm^3) was added over a period of 5 minutes and the reaction mixture stirred for a further 30 minutes at room temperature.

The reaction mixture was then poured into aqueous HCl (pH 4, 35 cm^3) and the aqueous layer thoroughly extracted with DCM (10 x 50 cm^3). Some yellow product precipitated and was filtered and washed with diethyl ether.

The combined organic layers were washed with water (3 x 50 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure to yield a yellow solid which was triturated with diethyl ether, filtered and combined with earlier product (287 mg, 72%), m.p. = 231°C, ν_{max} (nujol) cm^{-1} 3140(N-H), 1650 (C=O), 1015 (S=O); δ_H (d^6 DMSO) ppm 10.00 (1H, s, exchanges, N-$\underline{H}$), 8.60-7.27 (6H, m, aromatic protons), 4.58 (2H, ABq, J = 14Hz, $C\underline{H}_2$),2.64 (3H, s, $C\underline{H}_3$), 1.25 (3H, s, $C\underline{H}_3$); λ_{max} (95% ethanol) nm 334, 294, 275, 236, 191; m/z (low eV) 285 (M^+, 95%), 208 (77%), 194 (63%), 78 (100%), 63 (48%), (70eV) 285 (M^+, 17%), 208 (45%), 194 (47%), 78 (80%), 63 (100%); $C_{16}H_{15}NO_2S$: Requires C, 67.4; H, 5.3; N, 4.9%;

Found C, 66.2; H, 5.5; N, 4.8%.

3-*Acetyl*-1-*methylcarbazole* (170)

Method A: Reduction of the β-keto sulfoxide (202):

The β-keto sulfoxide (202) (132 mg, 0.46 mmol) was stirred in 10% aqueous THF (9 cm^3) and cooled with an ice bath.

Aluminium foil (142 mg, consecutively dipped into solutions of 2% aqueous mercury (11) chloride, ethanol and diethyl ether) was added to the reaction mixture and stirred for 30 minutes.

The reaction mixture was filtered, washed with THF and the THF removed at reduced pressure. The residue was partitioned between water (20 cm^3) and ethyl acetate (3 x 20 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography to yield the title compound as a colourless solid (84mg, 70%), recrystallised from DCM/pet.ether, m.p. = 178-180°C (lit[134] 193-194°C), R_f = 0.72 (pet.ether : ethyl acetate/50:50). ν_{max} ($CHCl_3$) cm^{-1} 3400 (N-H), 1650 (C=O), 1600 (C=C); δ_H (d^6 acetone) ppm 11.19-10.87 (1H, br.s, exchanges, N-H), 8.58-7.10 (6H, m, aromatic protons), 2.64 (3H, s, CH_3), 2.62 (3H, s, CH_3); λ_{max} (95% ethanol) nm 328, 288, 273, 236, 196; m/z (low eV) 223 (M^+, 100%), 208 (52%), (70eV) 223 (M^+, 62%), 208 (100%) ; $C_{15}H_{13}NO$: Requires C 80.7, H 5.8, N 6.3%; Found C 80.6, H 5.6, N 6.2%.

Method B Reaction of methyl lithium with the nitrile (169a):

To a solution of the nitrile (169a) (50mg, 0.24 mmol) in dry THF (6 cm^3), cooled to -78°C, under a nitrogen atmosphere, was slowly added a solution of methyl lithium (0.50 mmol, 1.5m in ether).

After the final addition, the reaction mixture was allowed to warm slowly to room temperature (at least 2h).

The red solution was then cooled with an ice bath and methanol (1 cm^3) added before the solvent was removed at reduced pressure to leave an orange solid.

This solid was dissolved in 50% aqueous acetic acid (9 cm^3) and gently refluxed for 30 minutes.

The solvent was removed at reduced pressure, saturated $NaHCO_3$ solution (20 cm^3) added and extracted with ethyl acetate (3 x 10 cm^3). The combined organic layers were washed with water (2 x 15 cm^3), brine (15 cm^3) and dried (Na_2SO_4). The solvent was removed and the residue purified by column chromatography to yield the title compound (170) as a colourless solid (53 mg, 98%), recrystallised from DCM/pet.ether, m.p. = 178°C.

Method C: From a mixture of the β-keto esters (193) and (168c):

An equal mixture of the β-keto esters (193) and (168c) (238mg, 0.80 mmol) was stirred in DMSO (1.5 cm^3) with water (16 mg, 0.88 mmol) and LiCl (37 mg, 0.88 mmol) at 120°C for 48h.

The mixture was then allowed to cool and was poured into H_2O (10 cm^3).

The aqueous layer was extracted with ethyl acetate (4 x 15 cm^3), the combined organic layers were washed with water (4 x 15 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was removed and the residue purified by column chromatography to yield two products.

The first product eluted had a $R_f = 0.40$ and the second product had a $R_f = 0.34$ (pet.ether : ethyl acetate/80:20).

The first product was identified as the ester (169b) (32 mg, 20%) and the second identified as the required title compound (170) (20mg, 15%).

3-*Cyano*-1,2,3,4-*tetrahydro*-1-*methylenecarbazole* (194)

A mixture of the tetrahydrocarbazole (168b) (300 mg, 1.08 mmol), water (25 mg, 1.39 mmol) and LiCl (45 mg, 1.08 mmol) was stirred in DMSO (2 cm^3) at 160°C, under a nitrogen atmosphere for 48h.

The reaction mixture was allowed to cool and then poured into water (20 cm^3).

The aqueous layer was extracted with DCM (4 x 15 cm^3) and the combined

organic layers were washed with water (3 x 15 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was removed and the residue purified by column chromatography to yield the title compound as a colourless solid (49 mg, 50%), recrystallised from ethyl acetate/pet.ether, m.p. = 145-148°C. R_f = 0.42 (pet.ether : ethyl acetate/80:20), ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2200 (C≡N), 1630 (C=C); δ_H ($CDCl_3$) ppm 8.18 (1H, s, N-H), 7.48-7.07 (4H, m, aromatic protons), 5.23 + 5.01 (2 x 1H, 2 x s, olefinic protons), 3.11 (3H, m, CH_2 + CHCN), 2.79 (2H, m, CH_2); λ_{max} (95% ethanol) nm 308, 242, 239, 206; m/z (low eV) 208 (M^+, 100%), (70eV) 208 (M^+, 100%), 207 (28%), 155 (43%), 154 (25%); $C_{14}H_{12}N_2$: Requires C, 80.8; H, 5.8; N, 13.5%; Found C, 80.4; H, 5.7; N, 13.2%.

3-*Cyano*-1-*methylcarbazole* (169a)

The crude product (194) (25 mg, 0.12 mmol) was stirred in dry benzene (2 cm^3) under a nitrogen atmosphere.

DDQ (30 mg, 0.13 mmol) was added and the dark green solution was heated at reflux for 14h.

The solvent was removed and the residue purified by column chromatography to yield the title compound as a pale yellow solid (20 mg, 75% for the two steps from (168b)).

Attempted Preparation of the imine (171)

Method A:

A solution of the ketone (170) (130 mg, 0.58 mmol) and aminoacetaldehyde dimethylacetal (367 mg, 0.38 cm^3, 3.5 mmol) in dry toluene (30 cm^3), containing p-toluene sulfonic acid (10 mg), was heated at reflux, using Dean-Stark apparatus, for 20h.

The reaction was followed by i.r. spectroscopy but no reaction was seen to be

taking place. The solvent was allowed to cool, washed with a saturated solution of $NaHCO_3$ (2 x 10 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure to yield a colourless oil (120 mg, 94%).

The oil was shown by ^1H n.m.r. analysis to be the starting ketone (170).

Method B:

The ketone (170) (5 mg, 0.02 mmol) was heated in aminoacetaldehyde dimethylacetal (40 mg, 0.38 mmol) for 7h. I.r. analysis of the reaction mixture indicated that no reaction had taken place.

3-*Formyl*-1-*methylcarbazole* (205)

To a stirred suspension of the nitrile (169a) (345 mg, 1.67 mmol) in dry benzene (5 cm^3), under a nitrogen atmosphere, was slowly added DiBAL (1.2 cm^3, 1.75 mmol, 1.5M). The suspension dissolved after the addition and the reaction mixture was stirred for 14h at room temperature, giving an orange precipitate.

Water (2 cm^3) was added to the reaction mixture, the benzene was removed at reduced pressure and the residue gently refluxed in dilute H_2SO_4 (10 cm^3) for 2h. The reaction mixture was allowed to cool and extracted with ethyl acetate (3 x 30 cm^3). The combined organic layers were washed with brine (30 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure.

The residue was purified by column chromatography (pet.ether/ethyl acetate) to yield the title compound as a pale yellow solid (340 mg, 94%), recrystallised from ethyl acetate/pet.ether, m.p. = 196°C (lit[187] 206-208°C); R_f = 0.70 (pet.ether : ethyl acetate/60:40); ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 1670 (C=O); δ_H (d^6 DMSO) ppm 11.79 (1H, br. s, exchanges, N-H), 10.01 (1H, s, CHO), 8.59 - 7.26 (6H, m, aromatic protons), 2.62 (3H, s, CH_3); λ_{max} (95% Ethanol) nm (ϵ) 329 (1300), 290 (2700) 274 (3300), 236 (3000), 200 (3100); m/z (low eV) 209 (M^+, 100%), (70eV) 209 (M^+, 100%), 208 (72%), 180 (46%); $C_{14}H_{11}NO$: Requires C, 80.4; H, 5.3; N, 6.7%; Found C, 80.0; H, 5.2; N, 7.1%.

3-[N-(2,2-Dimethoxyethyl)]imino-1-methylcarbazole (206)

A solution of the aldehyde (205) (346 mg, 1.66 mmol) and aminoacetaldehyde dimethylacetal (191 mg, 0.2 cm^3, 1.82 mmol) in dry benzene (40 cm^3) was heated to reflux, using a Dean-Stark trap.

The reaction was followed by i.r. spectroscopy, seeing the loss of the carbonyl stretch and the emergence of a new imine stretch at 1635 cm^{-1}.

After 4h, the reaction mixture was cooled and the solvent removed at reduced pressure to yield the title compound as an orange foam (472 mg, 96%).

Attempts to crystallise the product failed and it was used without further purification; ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 1635 (C=N); δ_H ($CDCl_3$) ppm 8.84 (1H, s, ArC<u>H</u>=N), 8.28 (1H, s, exchanges, N-<u>H</u>), 8.01-7.16 (6H, m, aromatic protons), 4.77 (1H, t, J = 5.3Hz, C<u>H</u>$(OCH_3)_2$), 3.83 (2H, d, J = 5.3Hz, HC = N-C<u>H_2</u>), 3.45 (6H, s, $(OC\underline{H_3})_2$), 2.38 (3H, s, C<u>H_3</u>); λ_{max} (95% ethanol) nm (ϵ) 314 (15000), 288 (41800), 274 (48100), 238 (38100); m/z (low eV) 296 (M^+, 37%), 75 (100%), (70eV) 296 (M^+, 8%), 75 (100%); $C_{18}H_{20}N_2O_2$; Acc. Mass : Calculated 296.3682; Found 296.1523.

3-[N-(2,2-Dimethoxyethyl)ethylamino]-1-methylcarbazole (207)

A solution of the imine (206) (150 mg, 0.51 mmol) in dry THF (3 cm^3) was stirred under a nitrogen atmosphere at -78°C.

To this solution was slowly added methyl lithium (0.7 cm^3, 1.11 mmol, 1.5M solution in diethyl ether). The mixture was kept at -78°C for 40 minutes and then allowed to warm slowly to O°C.

A solution of saturated ammonium chloride (10 cm^3) was added and the mixture thoroughly stirred for 10 minutes.

The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 10 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (pet.ether/ethyl acetate) to yield the amine (207) as a pale orange foam, (103 mg, 65%). The product was

used without further purification. R_f = 0.23 (pet.ether : ethyl acetate/60:40); ν_{max} ($CHCl_3$) cm^{-1} 3420 (carbazole N-H), 3260 (aliphatic N-H), 2860 (O-CH_3); δ_H ($CDCl_3$) ppm 8.20 (1H, s, carbazole N-H), 8.04-7.17 (6H, m, aromatic protons), 4.49 (1H, t, J = 5.5Hz, C<u>H</u>$(OCH_3)_2$), 3.92 (1H, q, J = 6.6Hz, CH_3C<u>H</u>NH), 3.35 + 3.29 (2 x 3H, 2 x s, 2 x O<u>C</u>H_3), 2.75-2.60 (2H, m, NHC<u>H</u>$_2$), 2.51 (3H, s, C-1 C<u>H</u>$_3$), 1.47 (3H, d, J = 6.6Hz, C<u>H</u>$_3$CHNH), 1.25 (1H, s, CH_3CHN-<u>H</u>); λ_{max} (95% ethanol) nm (ϵ) 339 (3500), 326 (3800), 295 (15000), 260 (19900), 249 (27000), 239 (36600); m/z (low eV) 312 (M^+, 27%), 297 (38%), 208 (100%), 99 (39%), (70eV) 208 (100%), 99(40%), 98 (28%); $C_{19}H_{24}N_2O_2$: Acc. Mass: Calculated 312.1848; Found 312.1836.

3-[N-(2,2-dimethoxyethyl)-N-(4-tosyl)ethylamino]-1- methylcarbazole (172)

Tosyl chloride (460 mg, 2.4 mmol) and sodium carbonate (240 mg, 2.6 mmol) were added to a solution of the amine (207) (144 mg, 0.46 mmol) in THF (2 cm^3) and water (4 cm^3).

The reaction mixture was stirred at ambient temperature for 48h. However, t.l.c. analysis (pet.ether : ethyl acetate/60:40) indicated the presence of starting material. Additional quantities of tosyl chloride (115mg, 0.6 mmol) and sodium carbonate (60 mg, 0.57 mmol) were added and the mixture stirred for a further 14h.

The reaction mixture was diluted with H_2O (14 cm^3) and extracted with ethyl acetate (3 x 10 cm^3). The combined organic layers were washed with 0.1N HCl (10 cm^3) H_2O (10 cm^3), saturated $NaHCO_3$ solution (10 cm^3), water (10 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure to give a pale yellow oil which was purified by column chromatography (pet.ether/ethyl acetate).

The title compound was isolated as a very pale yellow solid (185 mg, 84%), recrystallised from chloroform/pet.ether, m.p. = 153-154°C. R_f = 0.52 (pet.ether : ethyl acetate/60:40), ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 1590 (C=C); δ_H ($CDCl_3$) ppm 7.96 (1H, s, N-H), 7.87-6.81 (10H, m, aromatic protons), 5.24 (1H, q, J = 7.0Hz,

$CH_3\underline{C}HNTs$), 4.32 (1H, m, $\underline{C}H(OCH_3)_2$), 3.33+ 3.16 (2 x 3H, 2 x s, 2 x $OC\underline{H}_3$), 3.14 (2H, m, $NC\underline{H}_2CH$), 2.47 (3H, s, C-1 $C\underline{H}_3$), 2.40 (3H, s, tosyl $C\underline{H}_3$), 1.65 (3H, d, J = 7.1Hz, $C\underline{H}_3CHNTs$); λ_{max} (95% ethanol) nm (ϵ) 339 (6300), 324 (6900), 295 (27500), 260 (52700), 249 (69000), 239 (91000), 234 (81500), 201 (59100); m/z (low eV) 466 (M^+, 18%), 208 (100%), 75 (78%), (70 eV) 466 (M^+, 5%), 208 (87%), 75 (100%); $C_{26}H_{30}N_2O_4S$: Requires C, 66.9; H, 6.5; N, 6.0%; Found C, 66.6; H, 6.4; N, 5.8%.

1,2-Dihydro-1,5-dimethyl-2-(4-tosyl)-6H-pyrido[4,3-b] carbazole (208)

6N HCl (2 drops) was added to a stirred solution of the acetal (172) (97 mg, 0.21 mmol) in dry dioxan (2 cm^3), under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 16h.

The reaction mixture was heated at 60°C for 6h then added to 2N NaOH solution (15 cm^3) and extracted with ethyl acetate (3 x 15 cm^3).

The combined organic layers were washed with water (3 x 15 cm^3), brine (15 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure.

The residue was purified by column chromatography (pet. ether : ethyl acetate) to yield the title compound as a colourless oil (34 mg, 45%); R_f = 0.79 (pet.ether : ethyl acetate/70:30); ν_{max} ($CHCl_3$) cm^{-1} 3460 (N-H); δ_H ($CDCl_3$) ppm 7.96 (1H, s, N-$\underline{H}$), 7.93-6.97 (9H, aromatic protons), 6.80 (1H, dxd, J = 6.2Hz, TsN-$C\underline{H}$=CH), 6.31 (1H, dxd, J = 7.3Hz, TsN-CH=$C\underline{H}$), 5.35 (1H, m, $CH_3\underline{C}HNTs$), 2.45 (3H, s, C-5 $C\underline{H}_3$), 2.25 (3H, s,Ts$C\underline{H}_3$), 1.43 (3H, d, J = 6.6Hz, $C\underline{H}_3CHNTs$); λ_{max} (95% ethanol) nm (ϵ) 331 (7600), 258 (10600); m/z (low eV) 402 (M^+, 100%), 387 (34%), (70eV), 402 (M^+, 10%), 387 (30%), 247 (23%), 232 (30%), 91 (38%), 73 (26%), 42 (100%); $C_{24}H_{22}N_2O_2S$: Acc.Mass: Calculated 402.1391; Found 402.1400.

1,5-*dimethylpyrido*[4,3-*b*]*carbazole* (Olivacine) (2)

A solution of the tosyl compound (208) (20 mg, 0.05 mmol) was stirred in liquid ammonia (3 cm^3) at -78°C, under a nitrogen atmosphere.

Sodium metal (2.0 mg, 0.075 mmol) was added and the mixture was stirred for 40 minutes.

Ammonium chloride (10 mg) was added and the ammonia evaporated at room temperature, under a stream of nitrogen gas.The mixture was dissolved in methanol(5 cm^3) and 2N H_2SO_4(1 cm^3) and warmed at 50 °C for 1h. The methanol was then removed at reduced pressure.

The yellow residue was partioned between diethyl ether (5 cm^3) and 2N HCl (5 cm^3). The acidic layer was basified with solid NaOH (with cooling) and extracted with DCM (2 x 10 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated to yield the title compound as a yellow solid (8.5 mg, 70%). The product was found to be identical with an authentic sample.[190] m.p. = 315-320°C (lit[135] 320-324°C); R_f = 0.39 (DCM : ethanol: ammonia / 200:8:1); Acc. Mass. $C_{17}H_{14}N_2$: Calculated 246.1155; Found 246.1141.

1-(5-Benzyloxy-3-indolyl)-N,N-dimethylaminoethane (213)

A solution of acetaldehyde (217 mg, 4.93 mmol) in benzene (1 cm^3) was added to a mixture of 5-benzyloxyindole (1.0g, 4.48 mmol), dimethylaminehydrochloride (402 mg, 4.93 mol), K_2CO_3 (124 mg, 0.9 mmol), acetic acid (2 cm^3) and propenoic acid (1 cm^3) at -5°C.

The mixture was kept at -5°C for 1h then stirred at 4°C for 5 days.

The mixture was poured into iced water (20 cm^3) and extracted with diethyl ether (2 x 20 cm^3). The aqueous layer was made basic with 10 N NaOH and extracted with ethyl acetate (2 x 30 cm^3). The solvent was dried (Na_2SO_4) and removed at reduced pressure to give an off-white solid (0.43 g, 33%), which was recrystallised from ethyl acetate/pet.ether, m.p. = 93-96°C. R_f = 0.35 (DCM : methanol :triethylamine/98:2:1); ν_{max} (nujol) cm^{-1} 1580 (C=C); δ_H ($CDCl_3$) ppm 8.69 (1H, br s, N-H), 7.46-6.87 (9H, m, aromatic protons), 5.04 (2H, s, $OCH_2C_6H_5$), 3.80 (1H, q, J = 7.5Hz, $CH_3CH\,NMe_2$), 2.23 (6H, s, $N(CH_3)_2$), 1.48 (3H, d, J = 7.5Hz, CH_3CHNMe_2); λ_{max} (95% ethanol) nm (ϵ) 304 (7700), 294 (8400), 214 (31000); m/z (70eV) 249 (42%), 158 (66%), 91 (77%), 44 (100%), (C.I.) 292 (10%), 250

(100%), 249 (98%), 158 (48%), 91 (51%); $C_{19}H_{22}N_2O$: Requires C, 77.5; H, 7.5; N, 9.5%; Found C, 77.5; H, 7.5; N, 9.4%.

1-(5-benzyloxy-3-indolyl)aminoethane (219)

Phosphorus oxychloride (10.7 cm^3, 0.115 mol) was added dropwise to a cooled, stirred solution of N,N-dimethylacetamide (10.7 cm^3, 0.115 mol) in dry toluene (300 cm^3), under a nitrogen atmosphere.

After the addition, the mixture was stirred for 1h. 5-Benzyloxyindole (25.632g, 0.115 mol) was added and the mixture stirred for 17h.

On leaving to settle, the mixture separated into two layers. The top layer was decanted off and the bottom, orange layer was washed with diethyl ether (4 x 150 cm^3), decanting each time. The last traces of diethyl ether were removed at reduced pressure and the remaining orange oil was dissolved in analar methanol (800 cm^3). 0.88 NH_3 (16.5 cm^3) was added and the solution became pale green. Sodium borohydride (16.5g) was carefully added, portionwise, and the mixture stirred for a further 2.5h.

The solvent was removed at reduced pressure and the residue partitioned between 2N HCl (400 cm^3) and DCM (200 cm^3). The layers were separated, the aqueous layer made basic with solid KOH (with cooling) and extracted with DCM (3 x 200 cm^3).

The organic layers were combined, dried (Na_2SO_4) and evaporated to give a brown solid. Recrystallisation from ethyl acetate/pet. ether gave the title compound as a colourless solid (16.4g, 54%), m.p. = 125-128°C; R_f = 0.21 (DCM : methanol : triethylamine/96:4:2); ν_{max} (nujol) cm^{-1} 3345 (indole N-H), 3280 (aliphatic N-H); δ_H (d^6 DMSO) ppm 10.66 (1H, br s, exchanges, indole N-H), 7.49-6.76 (9H, m, aromatic protons), 5.08 (2H, s, $OCH_2C_6H_5$), 4.22 (1H, q, J = 7.5Hz, $CH_3CH\,NH_2$), 1.79 (2H, br s, exchanges NH_2), 1.26 (3H, d, J = 7.5Hz, $CH_3CH\,NH_2$);λ_{max}(95% EtOH)nm(ϵ) 274(10 100), 250(8 700); m/z (low eV) 249 (100%), (70eV) 249 (50%), 158 (81%), 130 (28%), 91 (100%); $C_{17}H_{18}N_2O$: Requires C, 76.7; H, 6.8; N, 10.5%; Found C, 76.3; H, 6.8; N, 10.3%.

Reaction of ethyl bromopyruvate with ethyl cyanoacetate

Ethyl cyanoacetate (0.64 cm^3, 6.02 mmol) was slowly injected into a stirred, cooled suspension of NaH (145 mg, 6.04 mmol) in dry DMF (8 cm^3), under a nitrogen atmosphere.

After the final addition, the ice bath was removed, and the mixture was stirred at ambient temperature for 30 minutes.

The resultant anion solution was then injected into a cooled solution of ethyl bromopyruvate (1.175g, 6.04 mmol) in dry DMF (10 cm^3).

The mixture was then stirred for 1h. T.l.c. analysis indicated a mixture of products. Consequently, the reaction was not worked up.

2-Bromomethyl-2-ethoxycarbonyl-1,3-dioxolane (226)

A solution of ethyl bromopyrurate (1.0g, 0.64 cm^3, 5.128 mmol), p-toluene sulphonic acid (1.27g, 6.66 mmol) and ethylene glycol (0.41g, 0.37 cm^3, 6.67 mmol) was heated in refluxing benzene (15 cm^3), using a Dean-Stark trap, for 16h.

The solution was allowed to cool and then washed with saturated $NaHCO_3$ solution (2 x 10 cm^3), water (3 x 10 cm^3), brine (10 cm^3) and dried ($MgSO_4$).

The solvent was removed at reduced pressure and the residue purified by bulb to bulb distillation, (110-112°C/0.1 mmHg).

The title compound was isolated as a colourless oil (580 mg, 47%); ν_{max} (thin film) cm^{-1} 1730 (C=O); δ_H ($CDCl_3$) ppm 4.27 (2H, q, J = 7.1Hz, $OC\underline{H}_2CH_3$), 4.18 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), 3.69 (2H, s, $BrC\underline{H}_2$), 1.33 (3H, t, J = 7.1Hz, $OCH_2C\underline{H}_3$); δ_C ($CDCl_3$) ppm 167.3 ($\underline{C}$=O), 129.7 (O-$\underline{C}$-O), 66.8 ($O\underline{C}H_2\underline{C}H_2O$), 61.9 ($O\underline{C}H_2CH_3$), 33.1 ($Br\underline{C}H_2$), 13.9 ($OCH_2\underline{C}H_3$); m/z (70eV) 167 (100%), 165 (100%), 121 (43%), 29 (32%), (C.I.) 241 [$(M+2)^+$,20%], 239 (M^+, 22%), 167 (88%), 165 (100%); $C_{17}H_{11}BrO_4$: Requires C, 35.2; H, 4.6%; Found C, 35.9; H, 4.6%.

Attempted reaction of ethyl cyanoacetate with the dioxolane (226)

Sodium metal (140 mg, 6.08 mmol) was completely dissolved in dry ethanol (10

cm^3), under a nitrogen atmosphere, keeping the temperature below 20°C.

Ethyl cyanoacetate (0.65 cm^3, 690 mg, 6.11 mmol) was added dropwise, again keeping the temperature below 20°C.

After the addition was complete, the ice bath was removed and the mixture stirred for 30 minutes.

The white suspension was then slowly transferred, *via* a cannula, into a cooled solution of the dioxolane (226) (1.45g, 6.07 mmol) in dry ethanol (11 cm^3). The solution was allowed to warm slowly to room temperature and stirred for 18h.

T.l.c. analysis (pet.ether : ethyl acetate/80:20) indicated that no product had formed.

The reaction mixture was then heated at reflux for 12h but again t.l.c. analysis indicated the presence of starting materials and no product.

The solvent was evaporated and the residue partitioned between ethyl acetate (25 cm^3) and water (20 cm^3). The separated organic layer was washed with water (2 x 20 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure to yield a pale yellow oil. ^1H n.m.r. analysis proved the oil to be a mixture of starting materials.

Attempted reaction between ethyl cyanoacetate and ethyl 3-bromo-2-hydroxyiminopropanoate(227)[157]

Method A:

A mixture of ethyl cyanoacetate (3.04 cm^3, 28.57 mmol), ethyl 3-bromo-2-hydroxyiminopropanoate (227)[157] (2.0g, 9.52 mmol) and anhydrous Na_2CO_3 (2.019g, 19.05 mmol) in dry DCM (20 cm^3) was stirred, under a nitrogen atmosphere, for 24h.

The reaction mixture was filtered through celite and the filtrate evaporated at reduced pressure.

^1H n.m.r. analysis of the crude oil showed a complex mixture, including the loss of the oxime O-H signal.

Method B:

Sodium metal (44 mg, 1.91 mmol) was completely dissolved in dry ethanol (4 cm^3), under a nitrogen atmosphere.

Ethyl cyanoacetate (216 mg, 0.20 cm^3, 1.91 mmol) was added, dropwise, with cooling. After the final addition, the ice bath was removed and the mixture stirred at ambient temperature for 30 minutes.

The suspension was then cooled, with an ice bath, and injected into a cooled solution of the oxime (227)[157] (400 mg, 1.91 mmol) in dry ethanol.

The reaction was stirred for 5 minutes before adding water (2 cm^3). The ethanol was removed at reduced pressure and the residue was partitioned between ethyl acetate (20 cm^3) and water (20 cm^3). The separated organic layer was washed with water (2 x 15 cm^3), brine (5 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure to yield a viscous yellow oil. ^1H n.m.r. analysis showed this product to be a mixture of compounds with no significant amount of the desired product.

Ethyl-3-bromo-2-methoxyiminopropananoate (229)

A mixture of methoxyamine hydrochloride (3.30 g, 39.46 mmol), ethyl bromopyruvate (7.70 g, 39.46 mmol), chloroform (120 cm^3) and methanol (80 cm^3) was vigorously stirred at ambient temperature for 16h.

The solvent was removed at reduced pressure, and the residue dissolved in DCM (100 cm^3). This was washed with water (50 cm^3), brine (50 cm^3) and dried (Na_2SO_4).

The solvent was evaporated at reduced pressure to give a clear oil which was purified by bulb to bulb distillation (120°C/1.2 mmHg) to yield the title compound as a colourless oil (7.8g, 88%). $R_f = 0.61$ (pet.ether : ethyl acetate/80:20); ν_{max} (thin film) cm^{-1} 1720 (C=O), 1592 (C=N); δ_H ($CDCl_3$) ppm 4.38 (2H, q, $J = 7.5Hz$, $OC\underline{H}_2CH_3$), 4.20 (2H, s, $BrC\underline{H}_2$), 4.17 (3H, s, $NOC\underline{H}_3$), 1.38 (3H, t, $J = 7.5Hz$, $OCH_2C\underline{H}_3$); λ_{max} (95% ethanol) nm (ϵ) 234 (3,600); m/z (low eV) 225 [$(M+1)^+$, 81%],, 223 (90%), 181 (64%), 179 (100%), 144 (60%), 135 (43%), (70eV), 225

[$(M+1)^+$, 37%), 223 (37%), 181 (60%), 179 (100%), 177 (34%), 144 (89%), 29 (100%); $C_{16}H_{10}BrNO_3$: Requires C, 32.2; H, 4.5; N, 6.3:; Found C, 31.7; H, 4.5; N, 5.6%.

Diethyl 2-cyano-4-methoxyimino-1,5-pentadioate (230) and *Diethyl 4-cyano-4-ethoxycarbonyl-2,6-di(methoxyimino)-1,7- heptadioate* (231)

Ethyl cyanoacetate (504 mg, 0.47 cm^3, 4.46 mmol) was added dropwise to a stirred, cooled suspension of sodium hydride (107 mg, 4.46 mmol), in dry DMF (10 cm^3), under a nitrogen atmosphere.

After the final addition, the ice bath was removed and the mixture stirred at ambient temperature for 30 minutes.

This pale green solution was then slowly injected, *via* a cannula, into a solution of the methoxime (229) (1.0g, 4.46 mmol) in dry DMF (10 cm^3).

The reaction mixture was stirred for 10 minutes at ambient temperature and then poured into water (60 cm^3).

The aqueous phase was extracted with ethyl acetate (60 cm^3) and the separated organic phase washed with water (3 x 30 cm^3) and brine (30 cm^3).

The solvent was dried (Na_2SO_4) and evaporated to give 972 mg (85%) of a yellow oil. T.l.c. analysis (hexane : ethyl acetate/2:1) showed the oil to be a mixture of 2 components.

The mixture was separated by column chromotography. The first compound eluted was shown to be the monoalkylated product (230). (R_f = 0.56, hexane : ethyl acetate/2:1). However, the product was contaminated by ethyl cyanoacetate but pure (230) could be obtained by bulb to bulb distillation (160°C/0.3 mmHg). Consequently, the diester (230) was obtained as colourless crystals (302 mg, 26%), recrystallised from chloroform/pet.ether, m.p. = 32-33°C. ν_{max} ($CHCl_3$) cm^{-1} 2250 (C≡N), 1745 (C=0), 1715 (C=O), 1600 (C=N); δ_H ($CDCl_3$) ppm 4.36 (2H, q, *J* = 7.5Hz, N=C-$CO_2\underline{CH_2}CH_3$), 4.26 (2H, q, *J* = 7.5Hz, NCCH$CO_2\underline{CH_2}CH_3$), 4.12

(3H, s, $NOC\underline{H}_3$), 4.02 (1H, t, J = 7.5Hz, $NCC\underline{H}CO_2Et$), 3.19 (2H, d, J = 7.5Hz, $CHC\underline{H}_2C{=}NOCH_3$), 1.37 (3H, t, J = 7.5Hz, $N{=}CCO_2CH_2C\underline{H}_3$), 1.32 (3H, t, J = 7.5Hz, $NCCHCO_2CH_2C\underline{H}_3$); λ_{max} (ethanol) nm (ϵ) 227 (4100); m/z (70eV), 225 (84%), 183 (100%), 155 (83%), 153 (52%), 137 (60%), 125 (94%), (C.I.) 257 [$(M+1)^+$, 100%], 211 (28%), 153 (22%), 125 (43%), 114 (96%); $C_{11}H_{16}N_2O_5$: Requires C, 51.6; H, 6.3; N, 10.9%; Found C, 51.2; H, 6.4; N, 10.7%.

The second compound eluted, R_f = 0.42 (hexane : ethyl acetate/2:1), was shown to be the dialkylated product (231). The product was obtained as a colourless oil and was purified by bulb to bulb distillation (220°C/0.4 mmHg), (527 mg, 60% gross). ν_{max} (thin film) cm^{-1} 2250 (C≡N), 1720 (C=O), 1690 (C=O), 1590 (C=N); δ_H ($CDCl_3$) ppm 4.35 (4H, q, J = 7.5Hz, 2 x $CH_3ON{=}CCO_2C\underline{H}_2CH_3$), 4.21 (2H, q, J = 7.5Hz, $NCCCO_2C\underline{H}_2CH_3$), 4.07 (6H, s, 2 x $NOC\underline{H}_3$), 3.28 (4H, ABq, J = 14Hz, 2 x $CH_3ON = CC\underline{H}_2$), 1.35 (6H, t, J = 7.5Hz, 2 x $CH_3ON = CCO_2CH_2C\underline{H}_3$), 1.30 (3H, t, J = 7.5Hz, $NCCCO_2CH_2C\underline{H}_3$); λ_{max} (ethanol) nm (ϵ) 227 (7200); m/z (loweV)399 (M^+, 37%), 368 (100%), 326 (63%), 243 (27%), 145 (91%), (70eV) 399 (M^+, 4%), 145 (100%), 29 (100%); $C_{17}H_{25}N_3O_8$: Requires C, 51.1; H, 6.3; N, 10.5%; Found C, 51.2; H, 6.6; N, 10.1%.

Ethyl 4,4-*dicyano*-2-*methoxyiminobutanoate* (232) and *Diethyl* 4,4-*dicyano*-2,6-*di(methoxyimino)*-1,7-*heptadioate* (233).

A solution of malonoitrile (221 mg, 3.35 mmol) in dry DMF (4 cm^3) was added, dropwise, to a stirred, cooled suspension of sodium hydride (80 mg, 3.35 mmol) in dry DMF (4 cm^3), under a nitrogen atmosphere.

After the final addition, the ice bath was removed and the mixture stirred at ambient temperature for 30 minutes.

The anion solution was then cooled again and injected into a cooled solution of the methoxime (229) (750 mg, 3.35 mmol) in dry DMF (8 cm^3), under a nitrogen atmosphere. The mixture was stirred at O°C for 1h and then added to water (50 cm^3). This was extracted with ethyl acetate (60 cm^3) and the organic layer washed with H_2O (3 x 30 cm^3), brine (40 cm^3) and dried (Na_2SO_4).

T.l.c. analysis of the residue revealed it to be a mixture of two components. The mixture was separated by column chromatography. The first product eluted (R_f = 0.51, hexane : ethyl acetate/2:1) was shown to be the monoalkylated product (232), purified by bulb to bulb distillation (150°C/1.1 mmHg). The product was isolated as a colourless oil (181 mg, 29%); ν_{max} (thin film) cm^{-1} 2230 (C≡N), 1700 (C=O), 1590 (C=N); δ_H ($CDCl_3$) ppm 4.38 (2H, q, *J* = 7.5Hz, $OC\underline{H}_2CH_3$), 4.32 (1H, t, J = 7.5Hz, $CH(CN)_2$), 4.17 (3H, s, $C{=}NOC\underline{H}_3$), 3.31 (2H, d, J = 7.5Hz, $C\underline{H}_2CH(CN)_2$), 1.37 (3H, t, *J* = 7.5Hz, $OCH_2C\underline{H}_3$);λ_{max}(95% EtOH)nm(ϵ) 254(3 100); m/z (70eV) 149 (20%), 136 (58%), 106 (100%), 29 (100%), (C.I.) 210 [$(M+1)^+$, 100%]; $C_9H_{11}N_3O_3$: Requires, C, 51.7; H, 5.3; N, 20.1%; Found C, 51.7; H, 5.5; N, 19.1%.

The second product eluted (R_f = 0.35, hexane : ethyl acetate/2:1) was an off white solid (312 mg, 54% gross), recrystallised from chloroform/pet.ether, m.p. = 83-85°C. This compound was characterised as the dialkylated product (233); ν_{max} ($CHBr_3$) cm^{-1} 1720 (C=O), 1600 (C=N); δ_H ($CDCl_3$) ppm 4.38 (4H, q, *J* = 7Hz 2 x $OC\underline{H}_2CH_3$), 4.18 (6H, s, 2 x $NOC\underline{H}_3$), 3.40 (4H, s, 2 x $C\underline{H}_2(CN)_2$), 1.41 (6H, t, *J* = 7Hz, 2 x $OCH_2C\underline{H}_3$);λ_{max}(95% EtOH)nm(ϵ) 252(10 100); m/z (70eV) 145 (60%), 71 (100%), (C.I.) 353 [$(M+1)^+$, 100%], 145 (40%); $C_{15}H_{20}N_4O_6$: Requires C, 51.1; H, 5.7; N, 15.9%; Found C, 51.4; H, 5.8; N, 15.7%.

Attempted preparation of Diethyl 2-cyano-4-oxopenta-1,5-dioate (220)

A mixture of the diester (230) (81 mg, 0.32 mmol), ammonium acetate (380 mg, 5 mmol) and 50% aqueous AcOH (2 cm^3) was stirred in DMF (5 cm^3), under a nitrogen atmosphere, whilst titanium trichloride (1.5 cm^3, 15% solution in 20% HCl) was added dropwise.

The mixture was stirred at ambient temperature for 18h but t.l.c. analysis (hexane : ethyl acetate/2:1) indicated that no product had formed.

The reaction mixture was then heated at 100°C for 90 minutes. T.l.c. indicated that the starting material had been consumed but the product was mainly baseline material.

The reaction mixture was cooled and extracted into diethyl ether (15 cm^3). The separated organic layer was washed with brine (10 cm^3), saturated $NaHCO_3$ solution (2 x 10 cm^3), water (5 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure.

^1H n.m.r. analysis of the residue showed loss of the $C\underline{H}_3$ methoxime singlet. However, the rest of the spectrum was very complicated and not indicative of the required compound.

Ethyl 2-cyano-but-2-enoate (240)

A solution of ethyl cyanoacetate (6.78 g, 6.4 cm^3, 0.06 mol) and acetaldehyde (3.35 cm^3, 0.06 mol) in glacial acetic acid (8 cm^3) was treated with a solution of piperidine (0.2 cm^3) in acetic acid (2 cm^3). The mixture was stirred at ambient temperature for 36h before the reaction mixture was added to water (100 cm^3). This aqueous phase was extracted with ethyl acetate (3 x 75 cm^3) and the combined organic layers were washed with saturated $NaHCO_3$ solution (2 x 100 cm^3), water (2 x 100 cm^3), brine (50 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure to yield a yellow oil which was purified by column chromatography to yield the title compound as a colourless oil (3.15g, 38%), R_f = 0.80 (pet.ether : ethyl acetate/70:30). The oil was further purified by bulb to bulb distillation (b.p. = 110°C/15mmHg, lit[162] 71-72°C/2.4mmHg); δ_H ($CDCl_3$) ppm 7.85 (1 H, q, J = 7.1Hz, $\underline{H}C$), 4.38 (2H, q, J = 7.3Hz, $OC\underline{H}_2CH_3$), 2.25 (3H, d, J = 7.2Hz, $\underline{C}H_3$), 1.37 (3H, t, J = 7.3Hz, $OCH_2C\underline{H}_3$).

Ethyl 3-(5-*benzyloxy*-3-*indolyl*)-2-*cyanobutanoate* (235)

Method A:

Ethyl cyanoacetate (850 mg, 7.52 mmol) was added, dropwise, to a cooled stirred suspension of NaH (180 mg, 7.52 mmol) in dry THF (15 cm^3). After the final addition, the ice bath was removed and the mixture stirred for 30 minutes.

A solution of the indole (219) (2.0 g, 7.52 mmol) in dry THF (20 cm^3) was added and the cloudy suspension stirred under a nitrogen atmosphere.

Iodomethane (0.47 cm^3, 7.52 mmol) was added, dropwise, and the mixture stirred for 24h.

The solvent was removed at reduced pressure and the residue partitioned between DCM (30 cm^3) and 2N HCl (30 cm^3). The separated aqueous layer was extracted with DCM (2 x 15 cm^3) and the combined organic layers were washed with water (2 x 30 cm^3), brine (20 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure and the residue purified by column chromatography to yield the title compound (463 mg, 17%) as a light brown oil R_f = 0.65 (pet.ether : ethyl acetate/70:30). The product was found to be a diastereomeric mixture (by ^1H n.m.r.) and could be used in subsequent reactions without further purification.$\delta_H(CDCl_3)$ppm 8.20 (1H, br. s, 2 x N-$\underline{H}$), 7.49 - 6.93 (9H, m , rest of aromatic protons), 5.11 (2H, s, 2 x O$\underline{CH_2}C_6H_5$), 4.26 (1.3H, q, J = 7.2 Hz, O$\underline{CH_2}CH_3$), 3.98 (0.7H, q, J = 7.15Hz, O$\underline{CH_2}CH_3$), 3.92 - 3.83 [2H, m, (2 x $CH_3\underline{CH}CH$) + (2 x $CH_3CH\underline{CH}$)], 1.57 (2H, d, J = 7.14 Hz, $\underline{CH_3}CHCH$), 1.53 (1H, d, J = 6.2 Hz, $\underline{CH_3}CHCH$), 1.28 (2H, t, J = 7.14 Hz, $OCH_2\underline{CH_3}$), 0.98 (1H, t, J = 7.14 Hz, $CH_2\underline{CH_3}$).

Crystallisation from ethyl acetate/pet.ether yielded a single diastereomer as colourless crystals, m.p. = 84-87°C; ν_{max} ($CDCl_3$) cm^{-1} 3450 (N-H), 2250 (C≡N), 1720 (C=O); δ_H ($CDCl_3$) ppm 8.25 (1H, s, exchanges with D_2O, N-$\underline{H}$), 7.48-6.90 (9H, m, aromatic protons), 5.08 (2H, s, O$\underline{CH_2}C_6H_5$), 4.24 (2H, q, J = 7.2Hz, O$\underline{CH_2}CH_3$), 3.83 (2H, m, $CH_3\underline{CH}$ + $\underline{CH}(CN)CO_2Et$), 1.51 (3H, d, J = 7.0Hz, $\underline{CH_3}CH$), 1.26 (3H, t, J = 7.2Hz, $OCH_2\underline{CH_3}$); λ_{max} (95% ethanol) nm (ϵ) 308 (2200), 295 (3200), 275 (4100); m/z (70eV) 362 (M^+, 41%), 271 (41%), 250 (100%), 159 (59%), 91 (82%), (loweV) 362 (M^+, 100%), 250 (33%); $C_{22}H_{22}N_2O_3$; Acc. mass : Calculated 362.1628; Found 362.1575; Requires C, 72.9; H, 6.1; N, 7.7%; Found C, 72.8; H, 6.1; N, 7.6%.

Method B:

A solution of ethyl cyanoacetate (307 mg, 2.72 mmol) and dimethyl acetylenedicarboxylate (0.33 cm^3, 2.72 mmol) in dry THF (10 cm^3) was added dropwise, to a cooled, stirred solution of (213) (800 mg, 2.72 mmol) in dry THF (10 cm^3), under a nitrogen atmosphere.

The reaction mixture was then allowed to warm slowly to room temperature. After 3h, the solvent was removed and the residue treated and purified as in Method A to yield the title diastereomeric mixture as a light brown oil (271 mg, 28%).

Method C

A solution of 5-benzyloxyindole (0.96 g, 4.31 mmol) and the olefin (240) (0.60 g, 4.31 mmol) in dry DCM (25 cm^3) was gently refluxed with K10 Montmorillonite clay (0.25g), under a nitrogen atmosphere.

After 48h, t.l.c. analysis (pet.ether : ethyl acetate/70:30) indicated the presence of required product (235) along with starting material.

The reaction mixture was allowed to cool, filtered and the solvent removed at reduced pressure. The residue was purified by column chromatography to yield the indole (235) (411 mg, 26%) along with starting material (1.02 g, 66%).

The same experiment was repeated but with heating in refluxing toluene as the solvent. The amount of (235) isolated was 423 mg (27%) with 811 mg (52%) of starting material recovered.

Method D:

The olefin (240) (1.20 g, 8.6 mmol) was added to a solution of 5-benzyloxyindole (0.9 g, 4.31 mmol) in acetic acid (3 cm^3) and acetic anhydride (1 cm^3), under a nitrogen atmosphere.

The mixture was stirred at 90°C for 8h and then stirred at ambient temperature for 16h.

The mixture was poured into water (30 cm^3) and extracted with ethyl acetate (2 x

50 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 50 cm^3), water (2 x 50 cm^3), brine (50 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure.

The light brown residue was purified by column chromatography to yield the title compound (235) as a light beige oil (1.04 g, 68%).

Attempted reaction between ethyl bromopyruvate and the indole (235)

A mixture of the indole (235) (111 mg, 0.307 mmol), K_2CO_3 (42 mg, 0.307 mmol) and ethyl bromopyruvate (60 mg, 0.307 mmol) in dry DMF (3 cm^3) was stirred, under a nitrogen atmosphere, for 1h.

T.l.c. analysis (pet.ether : ethyl acetate/60:40) indicated that no product had formed.

The mixture was then heated at 95°C for 24h. T.l.c. analysis indicated that no product had formed but that the ethyl bromopyruvate had decomposed.

Ethyl

5-(5-benzyloxy-3-indolyl)-4-cyano-4-ethoxycarbonyl-2-(methoxyimino)hexanoate

(234)

Method A:

Dimethylacetylenedicarboxylate (333 mg, 0.29 cm^3, 2.34 mmol) was added to a cooled, stirred solution of the gramine (213) (760 mg, 2.59 mmol) and the diester (230) (600 mg, 2.34 mmol) in dry THF (10 cm^3), under a nitrogen atmosphere. The ice bath was removed and the mixture was stirred at ambient temperature for 16h. The solvent was removed and the residue partitioned between 2N HCl (40 cm^3) and ethyl acetate (40 cm^3). The organic layer was washed with water (2 x 30 cm^3), brine (30 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl acetate). The title compound was isolated as a light brown oil (487 mg, 41%). ^1H n.m.r. indicated that the product was an equal mixture of two diastereomers. R_f =

0.32 (hexane : ethyl acetate/2:1); ν_{max} ($CDCl_3$) cm^{-1} 3450 (N-H), 2200 (C≡N), 1720 (C=O); δ_H ($CDCl_3$) ppm 8.44 + 8.31 (2 x 0.5H, 2 x br. s, 2 x N-H), 7.51- 6.87 (9H, m, other aromatic protons), 5.12 + 5.10 (2 x 1H, 2 x s, 2 x $OCH_2C_6H_5$), 4.37 (1H, q, J = 7.5Hz, OCH_2CH_3), 4.19 (1H, q, J = 7.5Hz, OCH_2CH_3), 4.07 + 3.93 (2 x 1.5H, 2 x s, 2 x $NOCH_3$), 3.68 (2H, m, 2 x CH_2), 3.43 (1H, m, 2 x CH_3CH), 1.67 (1.5H, d, J = 7.5Hz, CH_3CH), 1.46 (1.5H, d, J = 7.5Hz, CH_3CH), 1.21 (1.5H, t, J = 7.5Hz, OCH_2CH_3), 0.70 (1.5H, t, J = 7.5Hz, OCH_2CH_3); λ_{max} (95% ethanol)nm(ϵ) 307(10 100), 285(13 250), 276(15 800), 251(13 700); m/z (loweV) 505 (M^+, 30%), 249 (55%), 145 (38%), 106 (100%), (70eV) 505 (M^+, 2%), 354 (8%), 250 (50%), 145 (72%), 91 (100%), 43 (70%), 29 (100%); $C_{28}H_{31}N_3O_6$: Acc. mass: Calculated 505.2211; Found 505.2162.

Method B:

The indole (235) (150 mg, 0.41 mmol) and K_2CO_3 (57 mg, 0.41 mmol) were stirred in dry DMF (3 cm^3) under a nitrogen atmosphere.

The methoxime (229) (93 mg, 0.41 mmol) was added and the mixture stirred at ambient temperature for 24h. However, t.l.c. analysis (pet.ether : ethyl acetate/60:40) indicated the presence of starting material (27). A further amount of the methoxime (229) (50 mg, 0.22 mmol) was added and the reaction mixture was heated at 100°C for 7h.

The reaction mixture was allowed to cool and then poured into water (15 cm^3). The aqueous phase was extracted with ethyl acetate (2 x 20 cm^3) and the combined organic layers were washed with water (3 x 15 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was removed and the residue purified by column chromatography (pet.ether/ethyl acetate) to yield the title diastereomeric mixture (154 mg, 74%) as a light beige oil.

6-Benzyloxy-3-cyano-1,3-di(ethoxycarbonyl)-3,4-dihydro-4-methylcarbazole (241)

Method A:

A solution of the mixture (234) (175 mg, 0.35 mmol) in 4N HCl in dioxane (2 cm^3) was stirred under a nitrogen atmosphere for 36h.

The solution was neutralised with saturated $NaHCO_3$ solution, water (20 cm^3) was added and the mixture extracted with ethyl acetate (30 cm^3). The organic layer was washed with water (3 x 10 cm^3) and dried (Na_2SO_4).

The solvent was evaporated and the residue purified by column chromatography (pet.ether/ethyl acetate).

The title compound was isolated as a yellow oil (33 mg, 21%). ^1H n.m.r. analysis proved the product to be a mixture of 2 diastereomers; R_f = 0.56 (hexane : ethyl acetate/2:1); ν_{max} ($CHBr_3$) cm^{-1} 3440 (N-H), 2200 (C≡N), 1740 (C=O), 1710 (C=O); δ_H ($CDCl_3$) ppm 9.40 + 9.39 (2 x 0.5H, 2 x br. s, 2 x N-H), 7.52 - 6.93 (8H, m, aromatic protons), 6.92 + 6.70 (2 x 0.5H, 2 x s, 2 x olefinic protons), 5.11 (2H, s, 2 x $OCH_2C_6H_5$), 4.38 + 4.26 (2H, m, 2 x OCH_2CH_3), 3.94 (1H, m, 2 x CH_3CH), 1.52 (1.5H, d, J = 7.5Hz, CH_3CH), 1.41 (1.5H, t, J = 7.5Hz, OCH_2CH_3), 1.24 (1.5H, t, J = 7.5Hz, OCH_2CH_3), 1.08 (1.5H, d, J = 7.5Hz, CH_3CH); λ_{max}(95% EtOH)nm (ϵ) 284(2 700), 246(3 000); m/z (loweV) 458 (M^+, 100%), (70eV) 458 (M^+, 28%), 367 (25%), 149 (77%), 91 (100%); $C_{27}H_{26}N_2O_5$: Acc. Mass : Calculated 458.1840; Found 458.1885.

There was a complex mixture of other products from this reaction but these could not be identified.

Method B:

A solution of (234) (480 mg, 0.95 mmol) in $CHCl_3$ (6.5 cm^3) containing polyphosphate ester (20% w/v) was heated at reflux, under a nitrogen atmosphere, for 51h.

The solvent was removed at reduced pressure and the dark red residue was stirred with water (10 cm^3) for 30 minutes.

The aqueous layer was then extracted with ethyl acetate (2 x 10 cm^3) and the combined organic layers were washed with water (2 x 10 cm^3), brine (10 cm^3) and

dried (Na_2SO_4).

The solvent was evaporated at reduced pressure and the dark residue purified by column chromatography (pet. ether/ethyl acetate). Again, the reaction yielded a complex mixture of products and the required diastereomeric mixture of (241) was isolated as a yellow oil (91 mg, 22%).

6-Benzyloxy-3-cyano-1-ethoxycarbonyl-4-methylcarbazole (221)

A mixture of the dihydrocarbazole (241) (11 mg, 0.024 mmol), LiCl (1 mg, 0.024), water (0.43 mg, 0.024 mmol) and DMSO (0.5 cm^3) was heated at 100°C, under a nitrogen atmosphere.

After 26h, the mixture was allowed to cool and water (5 cm^3) added.

The mixture was extracted with ethyl acetate (3 x 20 cm^3) and the combined organic layers were washed with water (3 x 10 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl acetate) to yield the title compound as a pale yellow solid (4 mg, 45%), recrystallised from ethyl acetate/petrol, m.p. = 178-181°C; R_f = 0.66 (hexane : ethyl acetate/2:1); ν_{max} ($CHCl_3$) cm^{-1} 3350 (N-H), 2210 (C≡N), 1705 (C=O); δ_H ($CDCl_3$) ppm 10.20 (1H, br. s, N-H), 8.29 (1H, s, C-2H), 7.74-7.23 (8H, m, other aromatic protons), 5.20 (2H, s, $OCH_2C_6H_5$), 4.48 (2H, q, J = 7.1Hz, OCH_2CH_3), 3.05 (3H, s, CH_3), 1.48 (3H, t, J = 7.1Hz, OCH_2CH_3); λ_{max} (95% ethanol) nm (ϵ) 371 (1800), 294 (16600), 263 (10200), 250 (8100); m/z (low eV) 384 (M^+, 100%), 293 (63%), (70eV) 384 (M^+, 46%), 293 (89%), 247 (100%), 149 (21%), 91 (90%); $C_{24}H_{20}N_2O_3$: Acc. Mass : Calculated 384.1472; Found 384.1447; Requires C, 75.0; H, 5.2; N, 7.3%; Found C, 74.9; H, 5.1; N, 7.2%.

5-Benzyloxygramine (236)

A solution of 5-benzyloxyindole (8.9 g, 39.9 mmol) in dioxane (40 cm^3) was added, dropwise over 30 minutes, to a cooled, stirred mixture of 36% aqueous

formaldehyde (3.2 cm^3), 25% aqueous dimethylamine (8.8 cm^3), acetic acid (40 cm^3) and dioxane (40 cm^3).

The clear solution was stirred and cooled for 2h and then left to slowly warm to room temperature overnight (14h).

The reaction mixture was poured into water (500 cm^3) and the mixture filtered after stirring with charcoal and celite for 20 minutes.

The filtrate was made alkaline with an excess of dilute NaOH solution (400 cm^3) and the title compound precipitated as a colourless solid. The mixture was cooled and filtered to yield (32) (9.5 g, 85%) as an off-white solid which was dried, *in vacuo*, over P_2O_5.

The product was recrystallised from ethyl acetate to give colourless crystals, m.p. = 124-126°C (lit[188] 138-139°C), R_f = 0.29 (DCM ; methanol : triethylamine/96:4:2); δ_H ($CDCl_3$) ppm 8.91 (1H, br. s, N-H), 7.44 - 6.86 (9H, m, other aromatic protons), 5.00 (2H, s, $OCH_2C_6H_5$), 3.58 (2H, s, CH_2NMe_2), 2.27 (6H, s, $N(CH_3)_2$); m/z (70eV) 236 (42%), 235 (22%), 91 (100%), (low eV) 280 (M^+, 100%), 235 (79%); $C_{18}H_{20}N_2O$: Requires C, 77.1; H, 7.2; N, 10.0%; Found C, 76.8; H, 7.2; N, 9.9%.

Ethyl 3-(5-*Benzyloxy*-3-*indolyl*)-2-*cyanopropanoate* (237)

Method A:

A solution of ethyl cyanoacetate (806 mg, 0.76 cm^3, 7.14 mmol) and dimethyl acetylenedicarboxylate (0.88 cm^3, 7.14 mmol) in dry THF (20 cm^3) was slowly added to a stirred solution of 5-benzyloxygramine (236) (2.0 g, 7.14 mmol) in dry THF (20 cm^3), under a nitrogen atmosphere.

The resulting yellow solution was stirred at ambient temperature for 1h.

The solvent was removed at reduced pressure and the residue partitioned between 2N HCl (20 cm^3) and ethyl acetate (3 x 20 cm^3). The combined organic layers were washed with water (2 x 50 cm^3), brine (25 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure.

The residue was purified by column chromatography to yield the title compound as a pale yellow oil (480 mg, 19%). R_f = 0.45 (pet.ether : ethyl acetate/60:40); ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2250 (C≡N), 1735 (C=O); δ_H ($CDCl_3$) ppm 8.08 (1H, br. s. N-H), 7.50 - 6.92 (9H, m, aromatic protons), 5.11 (2H, s, $OCH_2C_6H_5$), 4.20 (2H, q, J = 7.1Hz, OCH_2CH_3), 3.78 (1H, dxd, J = 6.0Hz, $CH(CN)CO_2Et$), 3.39 (2H, m, $CH_2CH(CN)CO_2Et$), 1.23 (3H, t, J = 7.1Hz, OCH_2CH_3); λ_{max}(95% EtOH)nm(ϵ) 275(8 100), 250(5 800); m/z (low eV) 348 (M^+, 100%), (70 eV) 348 (M^+, 42%), 257 (74%), 236 (23%), 145 (26%), 91 (100%), 68 (43%), 29 (100%); $C_{21}H_{20}N_2O_3$: Acc. Mass: Calculated 348.1471; Found 348.1490.

Method B:

To a stirred solution of 5-benzyloxygramine (236) (7 g, 25 mmol) in dry THF (50 cm^3) and HMPA (5 cm^3), under a nitrogen atmosphere, was slowly added a solution of freshly distilled dimethyl sulphate (3.15g, 2.4 cm^3, 25 mmol) in dry THF (25 cm^3).

In a separate flask, a solution of ethyl cyanoacetate (2.6 cm^3, 24.5 mmol) in dry THF (35 cm^3) was slowly added to a cooled, stirred suspension of NaH (0.59 g, 25 mmol) in dry THF (15 cm^3), under nitrogen, in an ice bath.

After the addition was complete, the ice bath was removed and the reaction mixture stirred for 30 minutes.

The resultant suspension was then slowly transferred, *via* a cannula, into the methiosulfate reaction vessel. After the addition, the pale yellow solution was stirred for 2.5h before the solvent was removed and the residue partitioned between 2N HCl (125 cm^3) and ethyl acetate (125 cm^3).

The aqueous layer was extracted with ethyl acetate (2 x 50 cm^3) and the combined organic layers washed with water (2 x 75 cm^3), brine (50 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure.

T.l.c. analysis of the residue (pet.ether/ethyl acetate/60:40) indicated the presence of two compounds. These were separated by column chromatography.

The first compound eluted (R_f = 0.46, pet.ether/ethyl acetate/60:40) was a pale

yellow oil (1.93g, 24%) and was characterised as (237).

The second compound eluted (R_f = 0.38) was a colourless solid (3.39g, 47%) recrystallised from ethyl acetate/pet.ether, m.p. = 93°C. This compound was characterised as *ethyl* 2-C*yano*-2,2-*di*(5-*benzyloxy*-3-*indolyl*)*ethanoate* (238); ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2220 (C≡N), 1720 (C=O); δ_H ($CDCl_3$) ppm 8.14 (2H, br. s, 2 x N-H),7.47 - 6.86 (18H, m, aromatic protons), 5.09 (4H, s, 2 x $OCH_2C_6H_5$), 3.80 (2H, q, *J* = 7.1Hz, OCH_2CH_3), 3.41 (4H, ABq, *J* = 14.1Hz, 2 x $CH_2(CN)CO_2Et$), 0.74 (3H, t, *J* = 7.1Hz, OCH_2CH_3); λ_{max} (95% ethanol) nm (ϵ) 306 (7500), 295 (10650), 276 (13300), 248 (7800); m/z (70 eV) 91 (100%), (C.I.) 349 (76%), 348 (51%), 257 (25%), 236 (46%), 146 (42%), 91 (100%); $C_{37}H_{33}N_3O_4$: Requires C, 76.1; H, 5.7; N, 7.2%; Found C, 75.5; H, 5.7; N, 7.0%.

3-*Bromo*-2,2-*dimethoxypropanal* (252)

3-Bromo-2,2-dimethoxypropanol[164] (5.0 g, 25 mmol) was dissolved in dry ether (50 cm^3) at O°C, under a nitrogen atmosphere.

DCC (15.5 g, 75 mmol), anhydrous DMSO (1.95 cm^3, 27.5 mmol), dry pyridine (1.0 cm^3, 12.5 mmol) and trifluoroacetic acid (0.95 cm^3, 12 mmol) were added and the mixture stirred at O°C for 10 minutes before stirring at ambient temperature for 2h.

The ether was removed at reduced pressure and the residue distilled to yield the title compound (b.p. = 45°C/0.4 mmHg, lit[164] 30-32°C/0.2 mmHg) as a colourless oil (2.4 g, 45%). ν_{max} ($CHCl_3$) cm^{-1} 1745 (C=O); δ_H (d^6 DMSO) ppm 9.47 (1H, s, CHO), 3.71 (2H, s, $BrCH_2$), 3.27 (6H, s, 2 x OCH_3); m/z (70eV) 169 (81%), 167 (100%), 73 (42%), 43 (53%), (C.I.) 167 (100%), 165 (65%), 79 (34%).

3-*Bromo*-2,2-*dimethoxy*-N-*(propyl)iminopropane* (255)

A solution of n-propylamine (1.20 g, 1.7 cm^3, 20.3 mmol) and the aldehyde (252) (2.0 g, 10.2 mmol) in dry benzene (40 cm^3), under a nitrogen atmosphere, was

heated at reflux (using Dean-Stark apparatus) for 3.5h before being allowed to cool The benzene was removed at reduced pressure to leave a pale orange oil and colourless crystals. The oil was dissolved in ethyl acetate and the crystals filtered. The ethyl acetate was evaporated at reduced pressure to yield the title compound (1.9 g, 79%) as a pale orange oil. The compound was used without further purification; ν_{max} ($CHCl_3$) cm^{-1} 2800 (C-O), 1670 (C=N); δ_H ($CDCl_3$) ppm 7.55 (1H, s, HC=NPr), 3.58 (2H, s, $BrCH_2$), 3.53 (2H, m, $NCH_2CH_2CH_3$), 3.31 (6H, s, 2 x OCH_3), 1.71 (2H, m, $NCH_2CH_2CH_3$), 0.92 (3H, t, J = 7.3Hz, $NCH_2CH_2CH_3$); m/z (70eV) 167, 169 (40%), 88 (100%), 43 (42%), (C.I.) 208 (92%), 206 (100%), 169 (52%), 167 (54%), 158 (24%), 88 (100%).

3-*Bromo*-2,2-*dimethoxy*-N-*(propyl)propanamine* (251)

Method A:

Sodium cyanoborohydride (159 mg, 2.5 mmol) and the imine (255) (500 mg, 2.1 mmol) were stirred in dry methanol (10 cm^3), with 4A° molecular sieves, under a nitrogen atmosphere.

Acetic acid (1 cm^3) was added and the mixture stirred at ambient temperature for 20h before the methanol was removed at reduced pressure and the residue partitioned between 2N HCl (15 cm^3) and diethyl ether (15 cm^3).

The layers were separated and the aqueous layer further extracted with diethyl ether (2 x 10 cm^3).

The aqueous layer was then made basic with solid KOH (with cooling) before being extracted with DCM (3 x 30 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated to yield the title compound as a pale yellow oil (380 mg, 76%). (R_f = 0.61 (DCM : methanol : ammonia/200:8:1); ν_{max} ($CHCl_3$) cm^{-1} 3310 (N-H), 2820 (C-O); δ_H ($CDCl_3$) ppm 3.55 (2H, s, $BrCH_2$), 3.25 (6H, s, 2 x OCH_3), 2.86 (2H, s, $NCH_2CH(OMe)_2$), 2.62 (2H, t, J = 7.0Hz, $NCH_2CH_2CH_3$), 1.49 (3H, m, $NCH_2CH_2CH_3$ + N-H, exchanges with D_2O), 0.92 (3H, t, J = 7.3Hz, $NCH_2CH_2CH_3$); m/z (70eV) 88 (80%), 43 (100%), 33, 31 (100%), (C.I.) 160

(28%), 158 (40%), 128 (100%), 88 (100%).

Method B:

A solution of the aldehyde (252) (0.9 g, 4.57 mmol), n-propylamine (2.25 cm^3, 27.4 mmol), sodium cyanoborohydride (252 mg, 4 mmol) and acetic acid (1.5 cm^3) in dry methanol (15 cm^3) was stirred with 4A° molecular sieves, under a nitrogen atmosphere, at ambient temperature for 7h.

The solvent and excess propylamine were removed at reduced pressure and the residue treated as in Method A to yield the amine (251) as a pale yelllow oil (750 mg, 62%). The compound was used without further purification.

2-(N,N-*Dibenzylamino*)*ethanal*(250)

Dibenzylamine (7.0 g, 35.5 mmol) and glycidol (2.63 g, 35.5 mmol) were stirred at 100°C, under a nitrogen atmosphere, for 2h before being allowed to cool and diluted with $CHCl_3$ (100 cm^3).

The solution was then treated with $NaIO_4$ (0.1M in water, 42 cm^3), whilst being vigorously stirred.

After the addition was completed, the pH of the 2-phase system was adjusted to 8 with 2N NaOH.

The system was then vigorously stirred for 3h before the $CHCl_3$ layer was separated, dried (Na_2SO_4) and evaporated at reduced pressure to yield (250) as a light orange oil. The compound was unstable and was used immediately after synthesis. R_f = 0.89 (pet.ether : ethyl acetate/70:30); ν_{max} ($CHCl_3$) cm^{-1} 1725 (C=O); δ_H ($CDCl_3$) ppm 9.46 (1H, t, J = 1.7Hz, C<u>H</u>O), 7.36 - 7.09 (10H, m, aromatic protons), 3.65 (4H, s, 2 x C<u>H</u>$_2$C$_6$H$_5$), 3.13 (2H, d, *J* = 1.7Hz, NC<u>H</u>$_2$CHO); m/z (70eV) 210 (38%), 91 (100%), (C.I.) 240 [$(M+1)^+$, 65%], 210 (90%), 91 (100%).

N-(N',N'-dibenzyl-2-ethylamino)-3-bromo-2,2-dimethoxy-N-(propyl)propanamine (257)

A mixture of the amine (251) (0.9 g, 4.57 mmol), the aldehyde (250) (0.9 g, 4.57 mmol), sodium cyanoborohydride (252 mg, 4.0 mmol) and acetic acid (1.5 cm^3) were stirred in dry methanol (15 cm^3), with 4A° molecular sieves, under a nitrogen atmosphere.

After 120h, the solvent was removed at reduced pressure and the residue stirred with 2N HCl (40 cm^3) for 20 minutes.

The aqueous layer was extracted with diethyl ether (3 x 20 cm^3), made basic with solid KOH (with cooling) and then extracted with DCM (3 x 35 cm^3).

The combined DCM extracts were dried (Na_2SO_4) and evaporated to yield a pale yellow oil R_f = 0.44 (DCM : methanol : ammonia/200:8:1).

The yellow oil solidified when triturated with diethyl ether (5 x 30 cm^3) to yield a pale cream solid (1.11 g, 65%); ν_{max} ($CHCl_3$) cm^{-1} 2800 (C-O); δ_H ($CDCl_3$) ppm 7.40 - 7.29 (10H, m, aromatic protons), 4.44 (4H, AB, J = 12.6Hz, 2 x $C\underline{H}_2C_6H_6$), 3.75 (2H, t, $Bn_2NC\underline{H}_2CH_2$), 3.64 (4H, s, $BrC\underline{H}_2$ + $(MeO)_2CC\underline{H}_2N$), 3.22 + 3.19 (2 x 3H, 2 x s, 2 x $OC\underline{H}_3$), 2.85 (4H, m, $NC\underline{H}_2CH_2NBn_2$ + $NC\underline{H}_2CH_2CH_3$), 1.43 (2H, m, $NCH_2C\underline{H}_2CH_3$), 0.75 (3H, t, J = 7.2Hz, $NCH_2CH_2C\underline{H}_3$); λ_{max} (95% ethanol) nm (ϵ) 268 (2600), 262 (4500), 257 (6100); m/z (70eV) 295 (24%), 210 (68%), 208 (43%), 91 (100%), (C.I.) 465 [$(M+2)^+$, 4%], 463 (M^+, 5%), 419 (8%), 295 (61%), 210 (60%), 208 (22%), 91 (100%);

$C_{24}H_{35}BrN_2O_2$: Requires : C, 62.2; H, 7.6; N, 6.0%; Found C, 62.0; H, 7.7; N, 6.1%.

Attempted preparation of the ketone (249)

Method A:

A solution of the acetal (257) (116 mg, 0.25 mmol) in 98% formic acid (3 cm^3), under a nitrogen atmosphere, was heated at 85°C for 3 days.

The mixture was allowed to cool and then added to water (10 cm^3) . The solution was neutralised with saturated $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 15 cm^3) and the combined organic extracts were washed

with saturated $NaHCO_3$ solution (10 cm^3), water (15 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure to yield a brown oil (51 mg, 45%). ^1H n.m.r. analysis showed this oil to be the starting material (257).

Method B:

Iodotrimethylsilane (95 mg, 0.475 mmol) was stirred in dry DCM (1 cm^3), under a nitrogen atmosphere, at ambient temperature.

A solution of the acetal (257) (180 mg, 0.388 mmol) in dry DCM (2 cm^3) was added and the resulting mixture was stirred at ambient temperature for 90 minutes. T.l.c. analysis (DCM : methanol : ammonia/200:8:1) indicated the presence of a new product (R_f = 0.73) and the total consumption of starting material.

5% aqueous $NaHCO_3$ (5 cm^3) was added to the reaction mixture, followed by 10% aqueous $Na_2S_2O_5$ solution (5 cm^3). The layers were separated and the aqueous layer saturated with NaCl. The aqueous layer was then extracted with DCM (2 x 10 cm^3) and the combined organic layers dried (Na_2SO_4) and evaporated at reduced pressure to yield the acetal (258) (188 mg, 95%) as a colourless foam.

The reaction was repeated with 2.2 equivalents of iodotrimethylsilane. The product on work-up again proved to be the actal (258) (140 mg, 99%); ν_{max} ($CHCl_3$) cm^{-1} 2810 (C-O); δ_H ($CDCl_3$) ppm 7.35 - 7.22 (10H, m, aromatic protons), 4.33 (4H, ABq, J = 12.5Hz, 2 x $C_6H_5\underline{CH_2}$), 3.65 (2H, t, J = 5.7Hz, $Bn_2N\underline{CH_2}$), 3.59 [4H, s, $N\underline{CH_2}C(OMe)_2$ + $(MeO)_2C\underline{CH_2}I$], 3.17 + 3.14 (2 x 3H, 2 x s, 2 x $O\underline{CH_3}$), 2.77 (4H, m, $N\underline{CH_2}CH_2CH_3$ + $N\underline{CH_2}CH_2NBn_2$), 1.34 (2H, m, $NCH_2\underline{CH_2}CH_3$), 0.69 (3H, t, J = 7.3Hz, $NCH_2CH_2\underline{CH_3}$); m/z (70eV) 210 (76%), 91 (100%), 84 (63%), 49 (100%); (C.I.) 511 [$(M+1)^+$, 8%], 351 (23%), 295 (80%), 210 (63%), 91 (100%).

Attempted preparation of N-(3-Chloro-2-oxopropyl)phthalimide (263)

A solution of potassium phthalimide (1.13 g, 6.09 mmol) and 1,3-dichloroacetone (1.16 g, 9.13 mmol) in dry DMF (8 cm^3), under a nitrogen atmosphere, was heated at 100°C for 19h.

The reaction mixture was cooled and water (30 cm^3) added. This was extracted with ethyl acetate (3 x 40 cm^3) and the combined organic extracts were washed with water (4 x 40 cm^3), brine (10 cm^3) and dried (Na_2SO_4).
The solvent was evaporated at reduced pressure. ^1H n.m.r. analysis of the residue showed no significant amount of the required product but mainly a mixture of the starting materials.

N-(3-*Chloro*-2-*oxopropyl*)*phthalimide* (263)
N-(3-*Chloro*-2-*hydroxypropyl*)*phthalimide*[180] (50.0 g, 0.21 mol) was stirred in acetone (1000 cm^3) and cooled with an ice bath.
Jones Reagent [CrO_3(132 g), H_2O (380 cm^3) and conc. H_2SO_4 (110 cm^3)] was added, dropwise, in such a manner that the temperature did not rise above 30°C. After the addition was completed, the mixture was stirred at ambient temperature for 45 minutes.
The solvent was then evaporated at reduced pressure and iced water (3000 cm^3) added to the residue.
The green precipitate was filtered and washed with water until most of the green colour had been removed. The solid was then partitioned between ethyl acetate (500 cm^3) and water (250 cm^3). After separation the organic layer was washed with water (250 cm^3) and dried (Na_2SO_4).
The solvent was removed to yield the title compound (23.0g, 48%) as colourless crystals, recrystallised from ethyl acetate/pet.ether, m.p. = 124-126°C. R_f = 0.74 (pet.ether:ethyl acetate/60:40); ν_{max} ($CHCl_3$) cm^{-1} 1780 (C=O), 1720 (C=0); δ_H (d^6 DMSO) ppm 7.96 - 7.84 (4H, m, aromatic protons), 4.83 (2H, s, $C\underline{H}_2Cl$), 4.77 (2H, s, $NC\underline{H}_2C{=}O$); λ_{max} (95% ethanol) nm (ϵ) 294 (2800), 252 (1600); m/z (70eV) 160 (100%), (C.I.) 238 [$(M+1)^+$,81%], 160 (100%); $C_{11}H_8NO_3Cl$: Requires C, 55.6; H, 3.4; N, 5.9%; Found C, 55.6; H, 3.4; N, 6.0%.

Attempted reaction between the ketone (259) and the indole (235)

Method A:

A mixture of the ketone (259)[179] (0.5 g, 1.77 mmol), the indole (235) (0.64 g, 1.77 mmol), anhydrous K_2CO_3 (0.245 g, 1.77 mmol) and dry DMF (7 cm^3) was stirred at 65°C, under a nitrogen atmosphere.

After 40h, t.l.c. analysis (pet.ether : ethyl acetate/60:40) indicated that mostly starting material remained, with only a slight amount of slower running product. The reaction mixture was then heated to reflux. After 2h, t.l.c. analysis indicated that all the starting material had been consumed and the presence of a new, faster running spot.

The reaction mixture was cooled, added to water (60 cm^3) and extracted with ethyl acetate (2 x 40 cm^3). The combined organic extracts were washed with water (4 x 20 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was removed at reduced pressure and the residue purified by column chromatography to yield a white crystalline solid.

This compound was characterised as 5-benzyloxyindole (125 mg, 48%).

Method B:

A mixture of the ketone (259)[179] (0.5 g, 1.77 mmol), the indole (235) (0.6 4 g, 1.77 mmol), tetra n-butyl ammonium hydroxide (1.7 cm^3, 1.54M in water, 2.5 mmol) was stirred in DCM (5 cm^3) and water (2 cm^3) for 36h.

The solvent was removed at reduced pressure and water (10 cm^3) added. The mixture was extracted with diethyl ether (3 x 30 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure.

However, t.l.c. and ^1H n.m.r. analysis indicated that no reaction had occurred.

Method C:

A solution of the indole (235) (500 mg, 13.8 mmol) in dry DMF (5 cm^3) was slowly injected into a cooled suspension of NaH (33 mg, 1.38 mmol) in dry DMF (5 cm^3). After the final addition, the ice bath was removed and the mixture stirred at ambient temperature for 40 minutes.

The green, anion solution was then slowly injected into a cooled, stirred solution of the ketone (263) (328 mg, 1.38 mmol) in dry DMF (10 cm^3), under a nitrogen atmosphere.

The mixture was allowed to warm slowly to room temperature and then stirred for 14h.

T.l.c. analysis however showed no reaction had occurred.

The reaction mixture was heated at 60°C for 16h but again no reaction occurred.

Ethyl 2-*cyano*-4-*oxo*-5-(*N-phthalimidyl*)*pentanoate* (266)

Ethyl cyanoacetate (0.45 cm^3, 4.2 mmol) was added, dropwise, to a stirred, cooled suspension of NaH (100 mg, 4.2 mmol) in dry DMF (10 cm^3), under a nitrogen atmosphere.

After the final addition, the ice bath was removed and the reaction vessel stirred at ambient temperature for 30 minutes.

This solution was then slowly injected, *via* a cannula, into a cooled, stirred suspension of the ketone (263) (1.0 g, 4.21 mmol) in dry DMF (10 cm^3), under nitrogen.

After the addition, the mixture was allowed to warm slowly to room temperature. After 4h, the reaction mixture was added to water (120 cm^3) and extracted with ethyl acetate (2 x 75 cm^3). The combined organic extracts were washed with water (4 x 50 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was evaporated at reduced pressure to yield the title compound as a white solid. This solid was collected, washed well with pet.ether and recrystallised from ethyl acetate/pet.ether to yield colourless crystals, (1.09 g, 82%), m.p. =

140-142°C; R_F = 0.46 (pet.ether : ethyl acetate/60:40); ν_{max} ($CHCl_3$) cm^{-1} 1730 (C=O), 1720 (C=O); δ_H ($CDCl_3$) ppm 7.89-7.78 (4H, m, aromatic protons), 4.70 (2H, s, $NC\underline{H}_2$), 4.31 (1H, t, J = 5.5Hz, $NCC\underline{H}CO_2Et$), 4.21 (2H, q, J = 7.0Hz, $OC\underline{H}_2CH_3$), 3.40 (2H, d, J = 5.4Hz, $O{=}CC\underline{H}_2CH$), 1.28 (3H, t, J = 7.0Hz, $OCH_2C\underline{H}_3$); λ_{max} (95% ethanol) nm (ϵ) 294 (1900), 250 (1100); m/z (70eV) 160 (100%), (C.I.) 315 [$(M+1)^+$, 40%], 238 (62%), 160 (30%), 148 (100%); $C_{16}H_{14}N_2O_5$: Requires C, 61.1; H, 4.5; N, 8.9%; Found C, 60.7; H, 4.3; N, 8.7%.

5-(5-*Benzyloxy*-3-*indolyl*)-4-*cyano*-4-*ethoxycarbonyl*-1-(*N-phthalimidyl*)*pentan*-2-*one* (267)

A solution of the ketone (266) (12.8 g, 0.04 mol) and DMAD (5.0 cm^3, 0.04 mol) in dry THF (300 cm^3) was added, dropwise, to a cooled, stirred solution of the gramine (236) (11.47 g, 0.04 mmol) in dry THF (200 cm^3), under a nitrogen atmosphere.

After the final addition, the ice bath was removed and the reaction mixture stirred at ambient temperature for 3.5h.

The solvent was removed, at reduced pressure, and 2N HCl (25 cm^3) added. This was extracted with ethyl acetate (2 x 25 cm^3) and the combined organic layers were washed with water (2 x 40 cm^3), brine (10 cm^3) and dried (Na_2SO_4).

The solvent was removed, at reduced pressure, to yield an orange foam.

Crystallisation of this foam (ethyl acetate/pet.ether) produced a pale yellow solid (18.0 g, 80%), recrystallised from ethyl acetate/pet.ether. m.p. = 165-170°C; R_f = 0.26 (pet.ether : ethyl acetate/60:40); ν_{max} ($CHCl_3$) cm^{-1} 3460 (N-H), 2200 (w, C≡N), 1720 (C=O); δ_H (d^6 DMSO) ppm 10.28 (1H, br. s, N-$\underline{H}$), 7.84-7.75 (4H, m, phthalimidyl protons), 7.48-6.80 (9H, m, other aromatic protons), 5.08 (2H, s, $OC\underline{H}_2C_6H_5$), 4.59 (2H, d, J = 2.6Hz, $C\underline{H}_2$phth.), 4.02 (2H, q, J = 7.2Hz, $OC\underline{H}_2CH_3$), 3.55-3.34 (4H, m, 2 x $C\underline{H}_2$), 1.05 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); λ_{max} (95% ethanol) nm (ϵ) 294 (6000), 277 (6500), 253 (4000); m/z (70eV) 160 (100%), 43 (70%), (C.I.) 315 (100%), 204 (22%), 160 (85%), 148 (56%); $C_{32}H_{27}N_3O_6$: Requires C, 69.9; H, 5.0; N, 7.7%; Found C, 69.7; H, 4.9; N, 7.5%.

6-Benzyloxy-4-cyano-4-ethoxycarbonyl-1,2,3,4-tetrahydro-1-(N-phthalimidylmethylene)carbazole (269)

A mixture of the indole (267) (500 mg, 0.9 mmol) and p-toluene sulphonic acid (15 mg) was heated in refluxing toluene (60 cm^3), employing Dean-Stark apparatus. The dark green solution was allowed to cool after 30 minutes.

The mixture was washed with saturated $NaHCO_3$ solution (3 x 20 cm^3), water (30 cm^3) and brine (20 cm^3). The dried (Na_2SO_4) organic phase was then evaporated at reduced pressure. The residue was purified by column chromatography (pet.ether/ethyl acetate) to yield a yellow oil (464 mg, 96%).

^1H n.m.r. analysis indicated that this product was a mixture of the exo-cyclic and endo-cyclic double bond compounds, (269) and (268) respectively.$\delta_H(CDCl_3)$ppm; 8.99 (0.88H, s, N-H), 8.56 (0.12H, s, N-H), 7.85 - 7.71 (4H, m, phthalimidyl protons), 7.49 - 6.87 (8H, m, other aromatic protons), 6.63 (0.88H, s, endocyclic olefinic proton), 6.10 (0.12H, s, exocyclic olefinic proton), 5.05 (2H, s, 2 x $OCH_2C_6H_5$), 4.35 (0.24H, q, J = 7.2 Hz, OCH_2CH_3), 4.23 (1.76H, q, J = 7.14 Hz, OCH_2CH_3), 3.22 (1.76H, s, CH_2-phthalimide), 3.18 - 2.96 (2.24H, m, 3 x CH_2), 1.35 (3H, m, 2 x OCH_2CH_3).

However, crystallisation from ethyl acetate/pet.ether yielded a pale yellow solid m.p. = 240°C, dec., which was exclusively the exo-cyclic double bond product (269). The mixture was used in subsequent experiments. R_f = 0.64 (pet.ether : ethyl acetate/50:50); ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2210 (w, C≡N), 1720 (C=O), 1600 (C=C); δ_H (d^6 DMSO) ppm 10.65 (1H, br. s, exchanges with D_2O, N-H), 7.94 - 7.86 4H, m, phthalimidyl protons), 7.48 - 6.81 (8H, m, other aromatic protons), 6.18 (1H, s, olefinic proton), 5.10 (2H, s, $OCH_2C_6H_5$), 4.31 (2H, q, J = 7.3Hz, OCH_2CH_3), 3.44 + 3.21 (2 x 2H, 2 x ABq, J = 15.5Hz, 2 x CH_2), 1.29 (3H, t, J = 7.3Hz, OCH_2CH_3); λ_{max} (95% ethanol) nm (ε) 324 (5450), 252 (3600); m/z (low eV) 531 (M^+, 42%), 155 (100%), 120 (22%), (70 eV) 531 (M^+, 5%), 440 (8%), 155 (92%), 127 (54%), 99 (100%); $C_{32}H_{25}N_3O_5$: Requires C, 72.3; H, 4.7; N, 7.9%; Found C, 71.9; H, 4.7; N, 7.8%.

6-Benzyloxy-4-cyano-4-ethoxycarbonyl-1,2,3,4-tetrahydro-1-{N-[2-(methoxycarbo—nyl)-benzoyl]amino methylene}carbazole.(273)

A solution of the indole (269) (120 mg, 0.23 mmol) and p-toluene sulphonic acid (10 mg) in dry methanol (5 cm^3) was stirred, under a nitrogen atmosphere, for 24h.

The solvent was evaporated at reduced pressure and the residue purified by column chromatography (ethyl acetate/pet. ether) to yield the title compound as a bright yellow solid (74 mg, 93% based on recovered starting material), recrystallised from ethyl acetate/pet. ether, m.p. = 145 - 148°C. R_F = 0.73 (pet. ether : ethyl acetate/50:50); υ_{max} (nujol) cm^{-1} 3350 (N-H), 1720 (C=O), 1645 (C=O); δ_H (d^6 DMSO) ppm; 11.25 (1H, s, indole N-H), 10.30 (1H, d, J = 10.3Hz, amide N-H), 7.89-6.78 (13H, m, other aromatic protons + olefinic proton), 5.09 (2H, s, $OCH_2C_6H_5$), 4.30 (2H, q, J = 7.0Hz, OCH_2CH_3), 3.81 (3H, s, OCH_3), 3.54-2.88 (4H, m, 2 x CH_2), 1.31 (3H, t, J = 7.0Hz, OCH_2CH_3); λ_{max} (95% EtOH) nm (ϵ) 337 (32 500), 313 (27 500), 250 (20 000); m/z (70 eV), 279 (4%), 149 (30%), 119 (39%), 105 (43%); (C.I.) 391 (5%), 149 (42%), 100 (100%), 91 (78%); $C_{33}H_{29}N_3O_6$: Requires C, 70.3, H, 5.2, N, 7.5%; Found C, 70.1, H, 5.1, N, 7.4%.

6-Benzyloxy-4-cyano-4-ethoxycarbonyl-1,2,3,4-tetrahydro-1-{N-[2-(hydrazino)-benzoyl]aminomethylene}carbazole (274).

A mixture of (269) (320 mg, 0.60 mmol) and 85% aqueous hydrazine hydrate (0.5 cm^3) was heated in refluxing methanol (10 cm^3), under a nitrogen atmosphere, for 15 minutes.

The solution was cooled and the yellow precipitate was filtered, washed with water (5 cm^3) and dried over P_2O_5 (*in vacuo*) to yield the title compound as a bright yellow solid (138 mg, 41%), m.p. = 150 - 153°C (dec.). ^1H n.m.r. analysis indicated approximately 25% conversion to the corresponding methyl ester.

R_F = 0.19 (DCM : methanol : ammonia/200 : 8 : 1); υ_{max} ($CHCl_3$) cm^{-1} 3300 (br,m N-H), 1730 (C=O); δ_H (d^6 DMSO) ppm; 11.29 (1H, s, exchanges with D_2O, indole N-H). 10.32 (1H, d, exchanges with D_2O, J = 10.3Hz, ArCONHC=CH), 9.67 (1H, s, exchanges with D_2O, ArCONHNH_2), 7.60-6.79 (13H, m, other aromatic protons + olefinic proton), 5.10 (2H, s, $OCH_2C_6H_5$), 4.45 (2H, br, s, exchanges with D_2O, ArCONHNH_2), 4.39 (2H, q, J = 7.0Hz, OCH_2CH_3), 3.65-2.83 (4H, m, 2 x CH_2), 1.28 (3H, t, J = 7.0Hz, OCH_2CH_3); λ_{max} (95% EtOH)nm (ϵ) 337 (38 300), 300 (33 800), 247 (34 900); m/z (70 eV) 162 (100%), 104 (83%), (C.I.) 163 (100%), 162 (84%), 104 (58%), 76 (24%).

6-Benzyloxy-3-cyano-1-methylcarbazole (276).

A solution of (269) (212 mg, 0.4 mmol) and potassium cyanide (26 mg, 0.4 mmol) in hexamethylphosphoramide (5 cm^3) was heated at 125°C, under a nitrogen atmosphere, for 48h.

The mixture was allowed to cool and added to water (20 cm^3). This was extracted with ethyl acetate (2 x 20 cm^3) and the combined organic layers were washed with water (3 x 10 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl aacetate) to yield the title compound as a colourless oil. (15 mg, 12%); R_F = 0.68 (pet. ether : ethyl acetate/70 : 30); υ_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2220 (C≡N); δ_H (d^6 DMSO) ppm 11.63 (1H, s, N-H), 8.50 (1H, s, C-4H), 7.93 (1H, d, J = 2.6Hz, C-2H), 7.53 - 7.17 (8H, m, other aromatic protons), 5.19 (2H, s, $OCH_2C_6H_5$), 2.56 (3H, s, CH_3); m/z (low eV) 312 (M^+, 84%), 221 (49%), 147 (100%), 108 (40%), 91 (36%), (70 eV) 312 (M^+, 38%), 221 (75%), 147 (100%); $C_{21}H_{16}N_2O$: Calculated 312.1261; Found 312.1268.

Methyl 3-(Benzyloxy-3-indolyl)butanoate (285).

5-Benzyloxyindole (2.23 g, 0.01 mol), acetaldehyde (1.1 cm^3, 0.02 mol), Meldrum's Acid (1.44 g, 0.01 mol) and proline (58 mg) were stirred in acetonitrile (20 cm^3) for 28h, before the solvent was removed at reduced pressure and the residue was dissolved in pyridine (20 cm^3) and methanol (2 cm^3).

A small amount of copper powder was added and the mixture heated at reflux for 2.5h. The solvent was allowed to cool and then removed at reduced pressure. The residue was purified by column chromatography to yield the title compound as a light brown oil (360 mg, 12%); R_F = 0.60 (pet.ether : ethyl acetate/70 : 30); υ_{max} ($CHCl_3$) cm^{-1} 3460 (N-H), 1725 (C=O); δ_H ($CDCl_3$) cm^{-1} 8.14 (1H, s, N-H), 7.45 - 6.76 (9H, m, other aromatic prtoons), 5.04 (2H, s, $OCH_2C_6H_5$), 3.58 (3H, s, OCH_3) 3.62 - 3.49 (1H, m, CH_3CHCH_2), 2.79 - 2.46 (2H, m, CH_3CHCH_2), 1.34 (3H, d, *J* = 7.0Hz); λ_{max} (95% EtOH) nm (ϵ) 265 (5700), 248 (4350); m/z (low eV) 323 (M^+, 100%), 208 (24%), (70 eV) 323 (M^+, 21%), 232 (30%), 208 (49%), 205 (31%), 91 (56%); $C_{20}H_{21}NO_3$: Calculated 323.1520, Found 323.1511.

Attempted preparation of *5-(5-Benzyloxy-3-indolyl)-4-methoxycarbonyl-hexan-2-one* [(282),R_5 = H, R_{11}= CH_3]

A mixture of the ester (285) (350 mg, 1.08 mmol), chloroacetone (0.2 cm^3, 2.53 mmol) and sodium carbonate (299 mg, 2.16 mmol) was stirred in dry DMF (10 cm^3) for 55 minutes. However, t.l.c. analysis (pet. ether : ethyl acetate/ 70 : 30) indicated that no reaction had occurred. The mixture was heated at 100°C for 10h but again t.l.c. analysis indicated that no reaction had occurred.

Attempted preparation of *4-ethoxycarbonyl-5-(3-indolyl)hexan-2-one*

A solution of Ethyl 3-(3-indolyl)butanoate (286)[183] (610 mg, 2.64 mmol) in dry

THF (5 cm^3) was added to a solution of lithium diisopropylamide (5.28 mmol) in THF/pentane (12 cm^3) at -78°C.

The mixture was stirred, under a nitrogen atmosphere, for 1h before a solution of chloroacetone (0.50 cm^3, 5.8 mmol) in dry hexamethylphosphorous triamide (HMPT) (2 cm^3) was introduced at -78°C. The mixture was allowed to warm slowly to room temperature but t.l.c. analysis (pet.ether : ethyl acetate/60 : 40) indicated that no reaction had occurred.

3-(3-Indolyl)butanoic acid (287).

A solution of the ester (286) (350 mg, 1.51 mmol) in DMSO (1 cm^3) was added to a 50% aqueous solution of sodium hydroxide (1 cm^3). Benzyltriethylammonium chloride (3.5 mg, 0.015 mmol) and chloracetone (0.24 cm^3, 3.02 mmol) were added. The solution became quite hot and after 80 minutes, t.l.c. analysis (pet. ether : ethyl acetate/70 : 30) indicated total consumption of the starting ester (286) and the appearance of a more polar product.

Water (5 cm^3) was added and the mixture was extracted with diethyl ether (3 x 5 cm^3).

The aqueous layer was acidified with 2N HCl and extracted with diethyl ether (2 x 10 cm^3). The combined, second organic extracts were removed at reduced pressure.

The residue was purified by column chromatography (pet. ether/ethyl acetate) to yield the title compound as a light brown oil (200 mg, 65%), which crystallised overnight to afford light beige crystals; m.p. = 85-88°C; R_F = 0.18 (pet. ether :ethyl acetate/70 : 30); υ_{max} ($CHCl_3$) cm^{-1} 3460 (N-H), 3400 (br. O-H), 1700 (C=O); δ_H ($CDCl_3$) ppm 10.02 (1H, br. s, $CO_2\underline{H}$), 7.89 (1H, s, N-$\underline{H}$), 7.64 - 6.87 (5H, m, other aromatic protons), 3.65 - 3.52 (1H, m, $CH_3C\underline{H}CH_2$), 2.88 - 2.53 (2H, m,

$CH_3CHC\underline{H}_2$), 1.40 (3H, d, J = 7.0Hz, $C\underline{H}_3CHCH_2$); m/z (70 eV) 203(M^+,29%),144(100%);

$C_{12}H_{13}NO_2$, Calculated 203.0946,Found 203.0959.

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